ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 33 (O.S., Vol. XXXVII) NOVEMBER, 1950 NUMBER 5

CONTENTS

Page

Effects of Adrenocorticotropic Hormone in Pneumonia: Clinical, Bacteriological and Serological Studies. EDWARD H. KASS, SIDNEY H. INGBAR and MAXWELL FINLAND 1081

A Clinical Appraisal of Neomycin. BURTON A. WAISBREN and WESLEY W. SPINK 1099

Involvement of the Nervous System in Infectious Mononucleosis. THEODORE C. BERNSTEIN and HAROLD G. WOLFF 1120

Cation Exchange Resins in the Treatment of Congestive Heart Failure. SAMUEL H. HAY and J. EDWIN WOOD, JR. 1139

Patterns of Pulmonary Fibrosis as Related to Pulmonary Function. DAVID M. SPAIN 1150

Cytology of Sputum and Bronchial Secretions: Studies on 588 Patients with Miscellaneous Pulmonary Lesions. LEWIS B. WOOLNER and JOHN R. MCDONALD 1164

Criteria for and Interpretation of Normal Glucose Tolerance Tests. HERMAN O. MOSENTHAL and EILEEN BARRY 1175

The Association of Laennec's Cirrhosis with Diabetes Mellitus. MARTIN H. REINBERG and MORRIS LIPSON 1195

The Liver Biopsy: An Analysis of Pathological Findings in 75 Cases. JULIAN HOFFMAN and JULIUS ROSENTHAL 1203

Clinical Experiences with a New Mercurial Diuretic for Subcutaneous Administration. JOSEPH B. VANDER VEER, P. T. KUO and DAVID S. MARSHALL II 1215

Studies Relative to the Chemotherapy of Bacterial Endocarditis. M. H. NATHANSON and RUTH A. LIEBHOLD 1224

The Effects of Various Physical Procedures on the Circulation in Human Limbs. ROBERT W. WILKINS, MEYER H. HALPERIN and JULIUS LITTER 1232

The Changing Nature of Pneumonia. HOBART A. REIMANN 1246

The Inheritance of Spondylitis Rhizomelique (Ankylosing Spondylitis) in the K. Family. HERMAN H. RIECKER, JAMES V. NEEL and AVERY TEST 1254

Case Reports:

Frank Hematuria as a Manifestation of Infectious Mononucleosis. W. T. THOMPSON, JR. and CULLEN PITT 1274

Idiopathic Thrombophlebitis Migrans with Unusual Manifestations. PHILIP M. GOTTLIEB, DAVID TURNOFF, JOSEPH J. ZIMMERMAN and WILLIAM D. CHAMBLIN 1275

Neutropenia in a Patient Treated with a Mercurial Diuretic and Its Response to BAL. CHARLES E. BENDER, ROBERT J. HOXSEY and QUIN B. DEMARSH 1285

A Case of Polycythemia Vera Associated with the Wolff-Parkinson-White Syndrome. GEORGE A. WESTFALL, JR. and PHYLLIS J. BURDON 1290

Mycosis Fungoides with "Tumor d'Emblée": Report of a Case Treated with Nitrogen Mustard. THEODORE S. EVANS, ANTHONY P. CIPRIANO and ERWIN O. HIRSCH 1294

Generalized Primary Lymphangiomas of Bone: Report of a Case Associated with Congenital Lymphedema of Forearm. RAYMOND HARRIS and ANDREW G. PEANDONI 1302

Editorial—The Present Status of Electrocardiography 1314

Reviews 1323

College News Notes 1329

THE PRACTICAL APPLICATIONS
TO THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF DISEASE
OF THE CLINICAL INTERPRETATIONS OF
MODERN LABORATORY TESTS AND EXAMINATIONS

IN THE 2nd (OCTOBER 1949) EDITION OF

CLINICAL DIAGNOSIS
BY LABORATORY EXAMINATIONS

BY JOHN A. KOLMER, M.D., F.A.C.P.

Professor of Medicine, Temple University, School of Medicine and School of Dentistry; Director, Research Institute of Cutaneous Medicine, Philadelphia

Rewritten, heavily revised and somewhat enlarged by the inclusion of new text and illustrations, this new edition is up to date in every respect and will serve the physician and surgeon daily in his interpretation of the laboratory tests and examinations which are today so essential to prompt and accurate diagnosis. It supplies

THE CLINICAL INTERPRETATIONS OF

Blood Examinations; Urine Examinations; Blood Chemistry Examinations; Glucose Tolerance Tests; Kidney Function Tests; Basal Metabolic Rate and Iodine Tolerance Tests; Toxicological Examinations; Liver Function Tests and Examination of Bile; Examinations of Saliva and Sputum; Examinations of Stomach Contents; Duodenal Contents and of Pancreas Function Tests; Examination of Feces; Parasitological Examinations; Cerebrospinal Fluid Examinations; Bacteriological, Mycological and Serological Examinations; Serological Examinations in Syphilis; Immunological and Allergic Skin Tests; Examinations for Hormones and Vitamins; and Biopsy Examinations.

PRACTICAL APPLICATIONS IN DISEASES OF

The Blood and Hemopoietic System; Kidneys and Urinary System; Venereal Diseases; Stomach, Intestines and Pancreas; Liver and Biliary Tract; Cardiovascular System; Respiratory Tract; Metabolism; Vitamin Deficiency; Endocrine Glands; and Miscellaneous Infectious Diseases.

1240 Pages. 195 Diagnostic Illustrations with 20 in Color.
139 Diagnostic Summary Tables. $12.00

125th ANNIVERSARY 1825-1950

Published by
APPLETON-CENTURY-CROFTS, INC.
35 W. 32nd St., New York 1, N.Y.

Subscription per annum, net postpaid, $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1950.

Glomerular Nephritis

by Thomas Addis, M.D.

The major authority on this disease presents the results of twenty-five years of research and experimentation. Dr. Addis reveals the inadequacy of present therapy and sets forth a new direct method of diagnosis and treatment. The procedures are directed toward the general practitioner working with his nurse and patient. The treatment can be adequately administered in the doctor's office, complicated laboratory procedures having been entirely eliminated. The methods suggested are simple, rapid, and clinically sufficient.

338 pages

$8.00

Electroencephalography

Edited by Denis Hill, M.B., F.R.C.P., and Geoffrey Parr, M.I.E.E.

A Symposium on its Various Aspects

by

W. GREY WALTER, DENIS HILL,
W. A. COBB, D. WHITTERIDGE,
G. D. GREVILLE & M. E. HEPPENSTALL

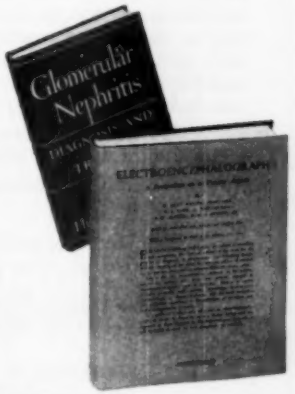
With a foreword by Prof. E. D. ADRIAN, O.M., F.R.S.

This is the first comprehensive textbook on the subject, written by authors who have been actively engaged in electroencephalography since its inception. Each is an expert in some particular field: physics, physiology, biochemistry, pharmacology, or clinical medicine; and the book embodies their collective experience in the technique of recording and in the interpretation of results.

As a guide to medical men who will use electroencephalography as an aid to diagnosis, or as a clinical background for engineers or those engaged in electrophysiological research, it will be found to cover the field completely yet concisely.

438 pages

$13.00



The Macmillan Company
60 Fifth Ave., New York 11, N. Y.

Please send and bill to me: _____ copies of

Glomerular Nephritis . . . Addis
Electroencephalography . . . Hill-Parr

NAME .....

ADDRESS .....

Henderson & Gillespie: TEXTBOOK OF PSYCHIATRY

Seventh edition. 1950. 752 *pages.* $7.75

By Sir David Henderson, M.D., F.R.C.P., Physician-Superintendent of the Royal Edinburgh Hospital for Mental Disorders, and Professor of Psychiatry, University of Edinburgh.

Since the previous edition many important advances have been made in the diagnosis and treatment of mental disorders. New methods of physical therapy have established themselves and it has become possible to evaluate such techniques as leucotomy, E.C.T., narcosis and other forms of direct if empiric attacks on the problem. It is now possible to publish the results of war time observation. More light has been thrown on the difficult question of psychopathic personality, medico-legal developments have been recorded and the intimate association of psychiatry with social factors has been assessed. This generally accepted standard British work in its field will appeal to all.

Burn: BIOLOGICAL STANDARDIZATION

Second edition. 1950. 450 *pages.* 77 *figures.* 84 *tables.* $6.75

By J. H. Burn, M.D., F.R.S., Professor of Pharmacology, University of Oxford.

This authoritative work treats of the estimation of the potency of medical substances which do not lend themselves readily to ordinary methods of chemical analysis. In the second edition a special feature has been made of the statistical implements which have so materially aided the laying of a systematic foundation for this important branch of pharmacology.

Lima: CEREBRAL ANGIOGRAPHY

1950. 234 *pages.* 181 *figures.* $8.75

By P. Almeida Lima, Professor of Neurology, Lisbon Faculty of Medicine.

An account of an improved technique for introducing into the cerebral circulation a medium furnishing contrast in radiography. This technique is free from the objections which make the older methods unsatisfactory. A special feature of this monograph is the large number of radiographs illustrating case-histories of intracranial tumours and other conditions localized by angiography. Sir Hugh Cairns has contributed a foreword.

OXFORD UNIVERSITY PRESS, INC., 114 Fifth Ave., New York 11, N.Y.

Hall-Brooke

(Established 1898)

Greens Farms (Westport) Connecticut

Only one hour from New York City

A licensed, private psychiatric hospital emphasizing the *treatment* of various psychoses, psychosomatic and emotional disorders, and the mental complications of toxic and metabolic conditions. . . . Selected cases of alcohol, barbiturate and other drug addictions likewise accepted. Special facilities for senile and arterio-sclerotic patients. . . . All private rooms, a number with private or semi-private baths. Remotely separated buildings insure suitable classification. . . . Rural New England setting; 120 acres beautifully wooded grounds.

Dynamically-oriented psychotherapy, electro-shock and insulin treatment administered by American Board certified psychiatrists.

Active Occupational and Recreational therapy department.

Sensible rates.

For literature and full information, write or phone

HALL-BROOKE

Greens Farms, Connecticut Telephone: Westport 2-5105

New York City office: 133 East 58th Street, Suite 709, Plaza 5-2570

Thursdays, 2–5 P.M.

GEORGE K. PRATT, M.D. - - - - Medical Director

4 Distinguished HOEBER Books

For The Busy Internist

Babkin's SECRETORY MECHANISM of the DIGESTIVE GLANDS

New 2nd Ed. This work, which correlates physiology of the digestive glands with their histologic structure, stresses pathologic functioning. It will help solve obscure digestive tract problems.

By B. P. BABKIN, M.D., *Research Prof. of Physiology, McGill Univ., Montreal;* 1056 pp., 233 illus., $20.00

Harris' BRUCELLOSIS (Clinical & Subclinical)

New 2nd Ed. This complete and practical book offers sound clinical help in recognizing the disease and distinguishing it from the many disorders it may simulate. It gives you the latest therapy available for both acute and chronic phases.

By HAROLD J. HARRIS, M.D., F.A.C.P., FELLOW, NEW YORK ACADEMY OF MEDICINE: 625 pp., 111 illus., 12 in full color. $10.00

Jolliffe, Tisdall & Cannon's CLINICAL NUTRITION

1950 Book This book, sponsored by the Food and Nutrition Board of the N.R.C., offers today's knowledge of nutrition, deficiency diseases and diet therapy organized for practical use in practice. 61 vivid color pictures help you detect obscure deficiencies. Official food value tables and dietary plans increase its everyday usefulness.

By 36 AUTHORITIES: 925 pp., 127 illus., 61 in full color. $12.00

Wolf, Grace & Wolff's THE HUMAN COLON

In Press This monograph reveals new facts about colonic functions stemming from first-hand observation of patients with exposed segments of colon. The authors present significant information on pharmacologic, physical, and emotional influences on the colon.

By STEWART WOLF, M.D., *Assoc. Prof. of Med.*, WILLIAM J. GRACE, M.D., *Assoc. Prof. of Med.*, and HAROLD G. WOLFF, M.D., F.A.C.P., *Prof. of Med. (Neurology), all at Cornell Univ. Medical College.* Approx. 220 pp., illus.

Order ON APPROVAL

PAUL B. HOEBER, Inc. AIM 1150
Medical Book Department of Harper & Brothers
49 East 33rd Street, New York 16, N. Y.

Send me on approval:

☐ Babkin's DIGESTIVE GLANDS....$20.00 ☐ Jolliffe's NUTRITION.....$12.00
☐ Harris' BRUCELLOSIS.....$10.00 ☐ Wolf, Grace & Wolff's COLON
☐ Charge my account ☐ Check Enclosed

Name.....
Address.....
City.....Zone.....State.....

Please Mention this Journal when writing to Advertisers

Two New Lea & Febiger Books

Cozen - Office Orthopedics

By Lewis Cozen, M.D., F.A.C.S.
Assistant Professor of Orthopedic Surgery, College of Medical Evangelists, Los Angeles, California

Procedures which general practitioners can use in the office treatment of orthopedic cases are described clearly and concisely in this book. It is based on the author's clinical and teaching experience and contains little that has not been tested and proved effective in clinics and in private practice. Dr. Cozen takes you right inside the office and depicts what is done for orthopedic patients. He describes the materials used for proper treatment and then goes directly into therapy for specific conditions affecting all parts of the body of both adults and children. ". . . fills a gap which exists in orthopedic information." —*U. S. Armed Forces Medical Journal.*

232 Pages. 156 Illustrations. $5.00

Burch - A Primer of Venous Pressure

By George E. Burch, M.D., F.A.C.P.
Henderson Professor of Medicine, Tulane University School of Medicine

This monograph is for those who have not previously given serious consideration to the application of measurements of venous pressure to clinical problems. The presentation is designed to arouse interest in these observations so that those unfamiliar with the subject might better understand and manage their patients. Indirect methods of measuring venous pressure which are adaptable to bedside use, and the direct method, which is the author's specialty, are explained fully. Special consideration is given to the normal values of venous pressure, including the factors which result in a variance in venous pressure in normal man.

174 Pages. 170 Illustrations. $4.00

Washington Square **LEA & FEBIGER** Philadelphia 6, Pa.

TRIGELMA*-H. M.

antispasmodic · antacid · adsorbent

plus + + +

+ Relative freedom from toxic side effects, as dryness of the throat, dilation of pupils, and increased heart rate.**
+ Synergistic antacid-adsorbent properties.**
+ Greater patient acceptability resulting from ease of administration and zesty fruit flavor.**

minus − − −

− Secondary acid rise characteristic of primary antacids.**
− Constipating effects.**
− Interference with iron absorption.**

STOCKED BY LEADING WHOLESALE DRUGGISTS

**Bibliography and Professional samples available on request.

TRIGELMA* — H.M. (BUFFINGTON) contains homatropine methyl bromide in a flavored mixture of concentrated aluminum hydroxide gel and magnesium trisilicate. Available in liquid and tablet form.

*TRIGELMA is a registered trade-mark of

BUFFINGTON'S INC.
PHARMACEUTICAL CHEMISTS
WORCESTER 8, MASS. U.S.A.

THERE IS A CAMBRIDGE ELECTROCARDIOGRAPH BEST FOR YOUR PURPOSE

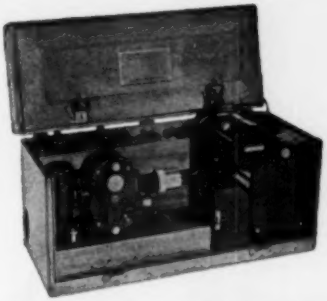
CAMBRIDGE Standard String Galvanometer Electrocardiographs assure the doctor of records that, because of their unquestioned accuracy, are universally accepted. These instruments record the minute heart-action currents directly without external amplification. All CAMBRIDGE Standard String Galvanometer instruments can be equipped to record heart sounds, pulse and electrocardiogram simultaneously.

The "SIMPLI-SCRIBE" Direct Writer is auxiliary to the Standard String Galvanometer instruments. It enables the Doctor or Institution to provide more complete Electrocardiographic service.

Send for descriptive literature

CAMBRIDGE INSTRUMENT CO., INC.
3715 Grand Central Terminal, New York 17, N. Y.
Chicago 12, 2400 West Madison Street
Philadelphia 4, 135 South 36th Street
Cleveland 15, 1720 Euclid Avenue

PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH



CAMBRIDGE "SIMPLI-TROL" PORTABLE MODEL

This instrument is ideal for the private office and small institution. It is light in weight and simple to operate, yet does not sacrifice fundamental accuracy or completeness of function the slightest degree. Entire equipment is in one case 8" x 19" x 10" and weighs only 30 pounds.

CAMBRIDGE MOBILE MODEL

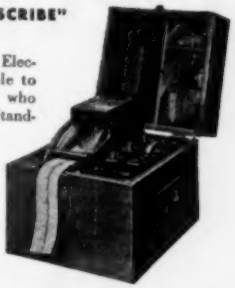
This is a cabinet type instrument designed for Hospitals and large Clinics. It will maintain its accuracy under the constant use and frequent abuse of busy Hospital service. It is fitted with two sturdy rubber-tired wheels and a swivel caster for convenient wheeling to the patient's bedside.

CAMBRIDGE RESEARCH MODEL

This model meets the exacting requirements of advanced study and teaching for an accurate, dependable, flexible multi-record instrument. Has two separate Einthoven string galvanometers as well as a third galvanometer of the d'Arsonval type. Other attachments available.

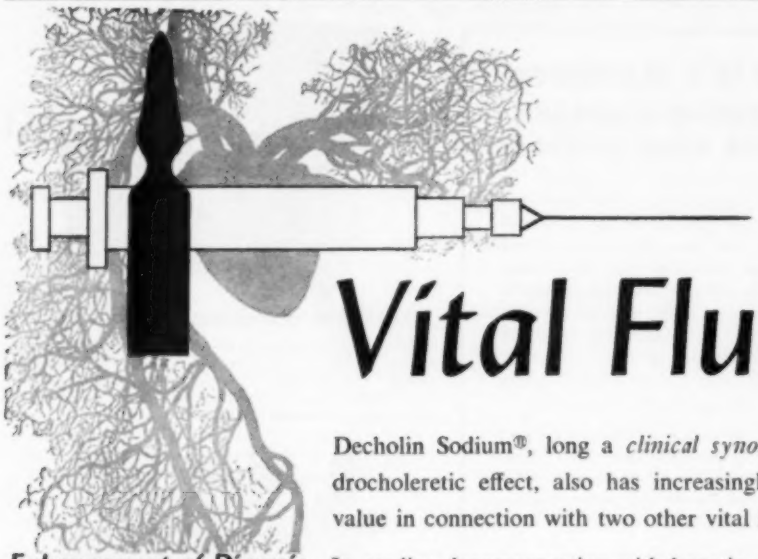
CAMBRIDGE "SIMPLI-SCRIBE" DIRECT WRITER

This direct writing, portable Electrocardiograph is available to Doctors and Institutions who already have CAMBRIDGE Standard String Galvanometer equipment. A fine supplemental instrument for gross pathology, screening, emergency consultation, etc. Size 10⅛" x 10⅜" x 11". Weighs only 28 pounds.



CAMBRIDGE ALSO MAKES ELECTROKYMOGRAPHS, PLETHSYMOGRAPHS, AMPLIFYING STETHOSCOPES, RESEARCH pH METERS, BLOOD PRESSURE RECORDERS, INSTRUMENTS FOR MEASURING RADIOACTIVITY, ETC.

CAMBRIDGE
ELECTROCARDIOGRAPHS



Vital Fluids

Decholin Sodium®, long a *clinical synonym* for hydrocholeretic effect, also has increasingly-recognized value in connection with two other vital fluids.

Enhancement of Diuresis. In cardiac decompensation with hepatic engorgement, Decholin Sodium given alone produces mild diuresis. More often it is administered simultaneously with mercurial diuretics to potentiate their action and reduce their dose.

Blood Circulation Time. Arm-to-tongue blood circulation time is reliably and relatively safely determined by injection of Decholin Sodium into a cubital vein. If desired, an arm-to-lung time test is readily included in the procedure by adding ether to the Decholin Sodium injection.

Decholin Sodium

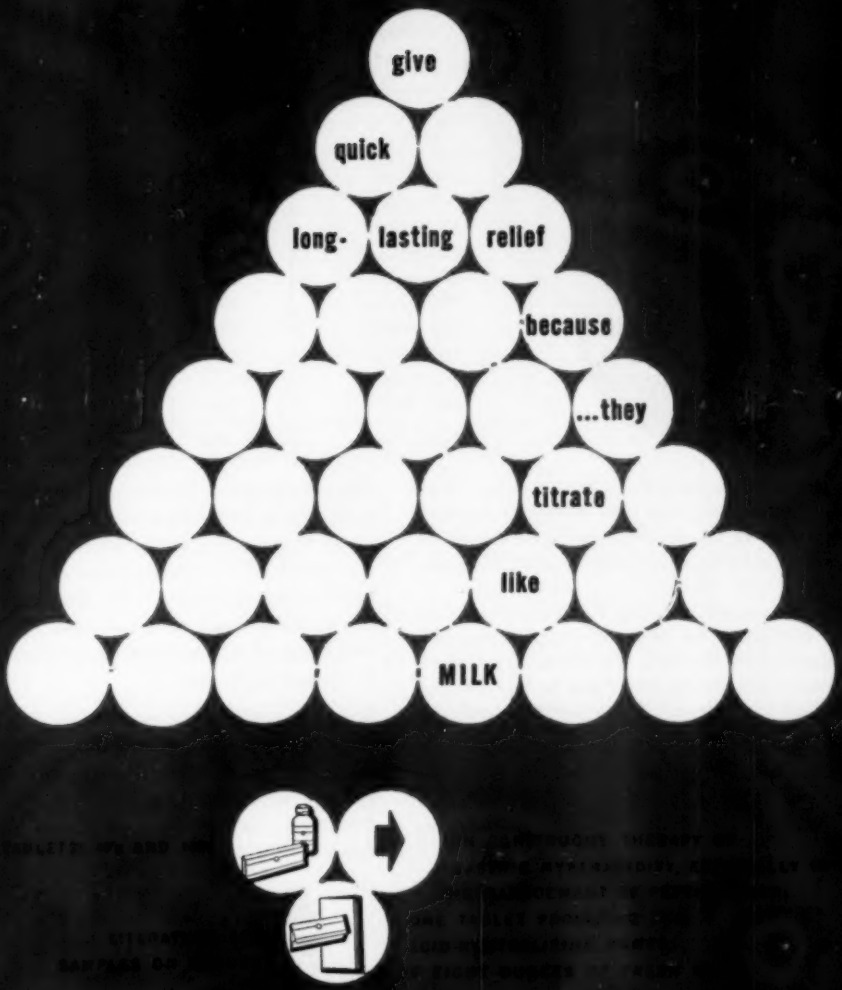
sodium dehydrocholate

supplied in 20% aqueous solution for intravenous administration. Available now in ampuls of 3 cc., 5 cc. and 10 cc.; boxes of 3 and 20 ampuls.

The booklets, "Decholin Sodium in Blood Velocity Determination" and "The Diuretic Action of Decholin Sodium" are now available—and will be sent upon your request.

AMES

AMES COMPANY, INC.
ELKHART, INDIANA


give
quick
long-
lasting
relief
because
...they
titrate
like
MILK

Amebiasis

OCCURS THROUGHOUT THE U. S. A.

Intestinal • Extra-Intestinal (Hepatic)

"The geographical distribution of amebiasis is world-wide."[1] "Although amebiasis is often considered a tropical disease, it is prevalent even in certain arctic regions."[2]

INCIDENCE OF AMEBIASIS IN THE UNITED STATES

STATE	NO. EXAMINED	NO. POSITIVE	% POSITIVE
New York[3]	350	34	9.7
Pennsylvania[4]	1060	43	4.1
Minnesota[5]	5000	535	10.7
Illinois[6]	4478	601	13.4
Oklahoma[7]	924	92	10.0
Washington[8]	1526	164	10.7
California[9]	1341	92	6.9
Louisiana[10]	4270	355	8.3
Tennessee[11]	20,237	2,305	11.4
New Mexico[12]	1284	190	14.8
Total	**40,470**	**4,411**	**10.9**

Intestinal. Comparative in vitro studies have shown that Milibis, the new intestinal amebacide, is one of the most powerful of the drugs commonly used against Endamoeba histolytica. In clinical tests Milibis has given excellent results in thousands of cases. In 82.6 per cent of those that could be followed parasitologically for prolonged periods, negative stools were obtained consistently after one to four courses of Milibis treatment.[13] There were virtually no side effects.

Dose for adults: 0.5 Gm. three times daily for seven days. If stools remain positive, course should be repeated. Supplied in tablets of 0.25 Gm., bottles of 50.

Extra-Intestinal. Aralen, an established antimalarial of relatively low toxicity, has been found remarkably effective in the treatment of extra-intestinal amebiasis (amebic hepatitis).[14-21] This discovery is particularly important because of the likelihood of extra-intestinal involvement in chronic amebiasis.

Dose for adults: 4 tablets daily in divided doses for two days, followed by 2 tablets daily for two to three weeks. Administer before, after or together with Milibis treatment. Supplied in tablets of 0.25 Gm., bottles of 100 and 1000.

MILIBIS®
Bismuth Glycolylarsanilate

ARALEN®
DIPHOSPHATE
Chloroquine Diphosphate

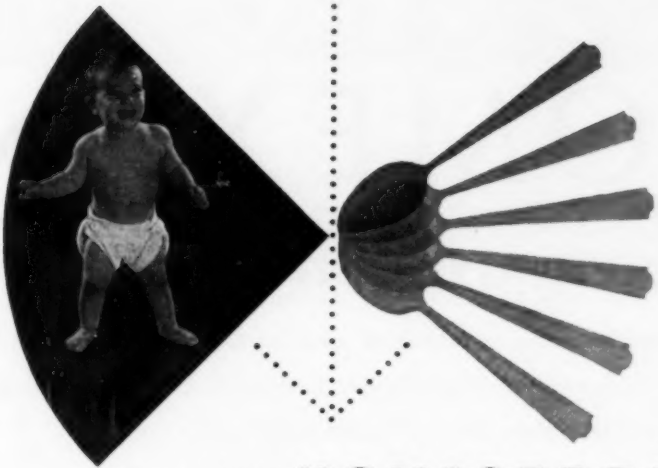
Write for detailed information.

Winthrop-Stearns INC.
NEW YORK, N. Y. WINDSOR, ONT.

1. Craig, C. F.; 2. Almy, T. P.; 3. Towse, R. C., et al.; 4. Wenrich, D. H., et al.; 5. Sanford, M. F.; 6. Spector, B. K.; 7. McMullen, D. B., and Gray, J. K.; 8. Cresswell, S. M., and Wallace, C. E.; 9. Wight, T.; 10. Faust, E. C., and Headlee, W. H.; 11. Meleney, H. E., et al; 12. Spector, B. K., and Hardy, A. V.; 13. Berberian, D. A.; 14. Conan, N. J.; 15. Shookhoff, H B.; 16. Sademan, W. A.; 17. Murgatroyd, F., and Kent, R. P.; 18. Basnuevo, J., and Estarli, E. G.; 19. D'Antoni, J. S.; 20. Manson-Bahr, P.. 21. Emmett, J. Full bibliography on request.

Milibis, trademark – Aralen, trademark reg. U. S. & Canada

how to get the most out of vitamins



The natural oil globules in **HOMICEBRIN**

(Homogenized Vitamins A, B_1, B_2, C, and D, Lilly), as in milk, are so finely subdivided that they are easily and completely assimilated. Such minute particles readily surrender their vitamin content to the delicate digestive tract of even the smallest infant. The essential water-soluble factors further round out this formula to give young patients full protection from vitamin deficiencies.

The new pint-size economy package reduces the cost of the daily dose in early infancy to less than two cents.

DIABETES DETECTION WEEK

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

Complete literature on Lilly vitamin products for prescription use is available from your Lilly medical service representative or will be forwarded upon request.

a most significant advance

TROMEXAN T. M.

ethyl acetate

new, safer, oral anticoagulant

Throughout the exhaustive studies on TROMEXAN, involving many hundreds of cases, this new anticoagulant has proved singularly free from the dangers of hemorrhagic complication. Other advantageous clinical features of TROMEXAN are:

1 ***more rapid therapeutic response***
(therapeutic prothrombin level in 18-24 hours);

2 ***smooth, even maintenance of prothrombin level***
within therapeutic limits;

3 ***more rapid return to normal***
(24-48 hours) after cessation of administration.

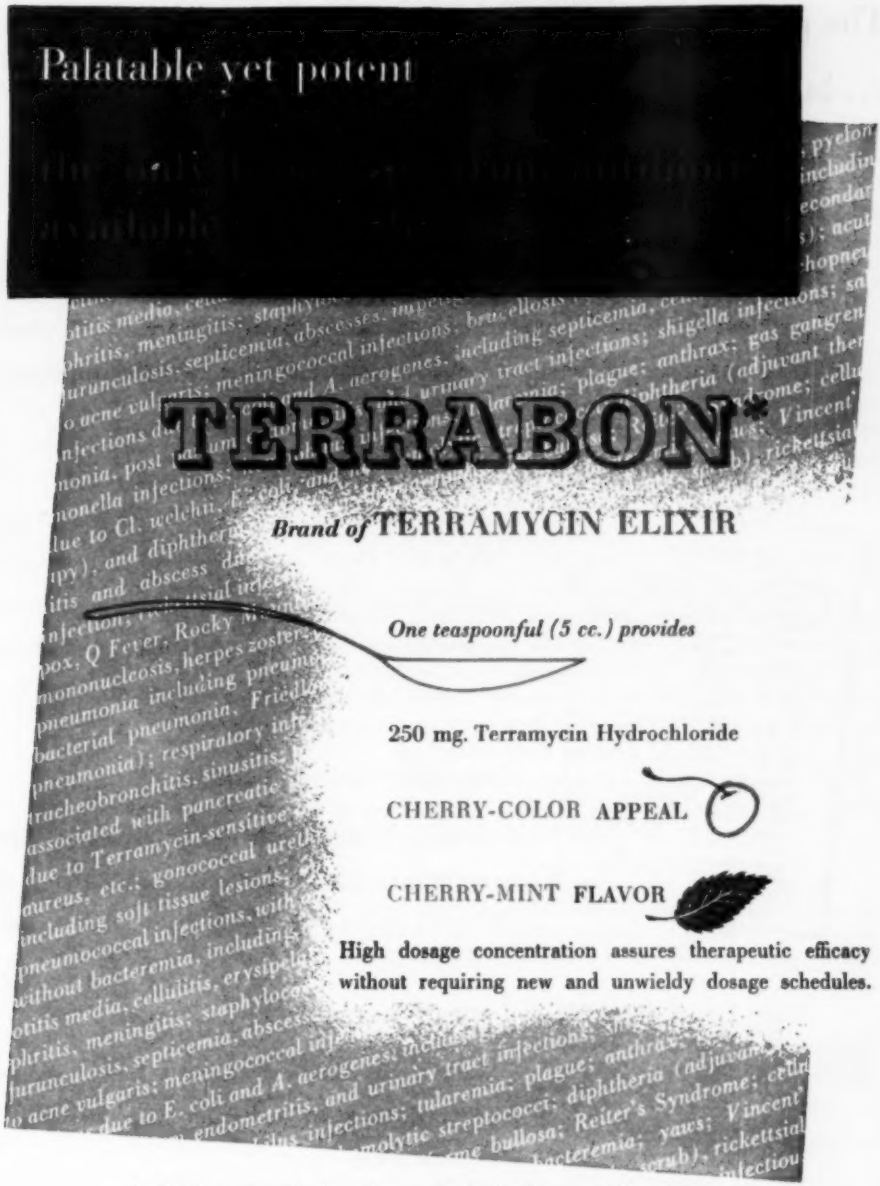
In medical and surgical practice . . . as a prophylactic as well as a therapeutic agent . . . TROMEXAN extends the scope of anticoagulant treatment by reducing its hazards.

Detailed Brochure Sent on Request.

TROMEXAN (brand of ethyl biscoumacetate): available as uncoated scored tablets, 300 mg., bottles of 50 and 250.

Geigy

GEIGY COMPANY, INC.
Pharmaceutical Division, 89-91 Barclay St., New York 8, N. Y.


Palatable yet potent
TERRABON*
Brand of TERRAMYCIN ELIXIR
One teaspoonful (5 cc.) provides
250 mg. Terramycin Hydrochloride
CHERRY-COLOR APPEAL
CHERRY-MINT FLAVOR
High dosage concentration assures therapeutic efficacy without requiring new and unwieldy dosage schedules.

Available at prescription pharmacies in bottles containing 1 fl. oz.

*Trade Mark

Antibiotic Division Pfizer CHAS. PFIZER & CO., INC., Brooklyn 6, N. Y.

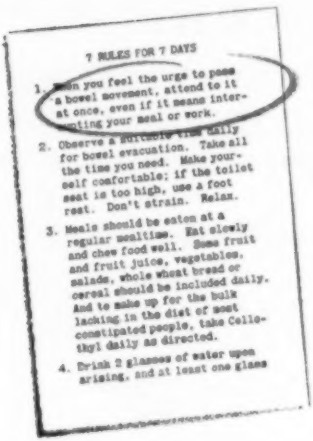
The physician knows

. . . but the patient too seldom appreciates

the penalty of postponement.

"Failure to answer the call to stool"[1] is one of the most common causes of constipation. As rectal reflexes are dulled, fecal accumulation, inspissation and subsequent atony make evacuation progressively more difficult.

An aid to patient-education:



7 RULES FOR 7 DAYS

1. When you feel the urge to pass a bowel movement, attend to it at once, even if it means interrupting your meal or work.
2. Observe a definite time daily for bowel evacuation. Take all the time you need. Make yourself comfortable; if the toilet seat is too high, use a foot rest. Don't strain. Relax.
3. Meals should be eaten at a regular mealtime. Eat slowly and chew food well. Some fruit and fruit juice, vegetables, salads, whole wheat bread or cereal should be included daily. And to make up for the bulk lacking in the diet of most constipated people, take Cellothyl daily as directed.
4. Drink 2 glasses of water upon arising, and at least one glass

Prompt response to physiologic urge is one of the "7 Rules for 7 Days," outlined in a simple leaflet designed for better patient-understanding, to overcome what are called "improper habits . . . which either singly or combined" cause constipation.[1]

Available to physicians:

Pads of the "7 Rules" may be had on request. Just write "7 Rules" on a prescription blank and send to Chilcott Laboratories, Morris Plains, New Jersey.

An aid to physiologic correction:

Cellothyl, physiologically correct bulk, may be prescribed to assist in establishing the normal peristaltic reflex.

Please Mention this Journal when writing to Advertisers

A high percentage of good results obtained both in clinic and private practice

In 80 to 92% of patients in private practice[2,3] constipation was corrected with Cellothyl. Even in obstinate clinic-treated cases,[1] it was found that *years of constipation can be corrected in a matter of days* with Cellothyl.

These gratifying results can be duplicated in your own practice by incorporating Cellothyl Tablets (physiologically correct colloid) into a sensible two-part anticonstipation regimen such as these investigators found so successful.

Part I PHILOSOPHY OF CORRECTION

To assure a proper "mental attitude . . . the simple rules of bowel hygiene"[3] are explained. Effort is directed against poor diet, cathartic abuse, etc.,—and the fact stressed that the effect of lifelong habits which *cause* constipation cannot be nullified overnight. As a reminder of your advice, you may want to give the patient a copy of the leaflet "7 Rules for 7 Days," which is available on request.

Part II PHYSIOLOGY OF CORRECTION

Since explanation and advice often fail to alter deeply ingrained habits,[1-3] physiologic therapy with Cellothyl is an important part of the anticonstipation program.

Cellothyl is physiologically correct: following the normal digestive gradient, Cellothyl passes through the stomach and small intestine as a fluid, then thickens to a smooth gel in the colon to provide bulk where bulk is needed for soft, moist, easily passed stools.

Because of the unhurried, physiologic manner in which Cellothyl acts, enough time must be allowed for it to reach the colon before the first normal well-formed stool results. With sufficient bulk to stimulate intestinal motility and mass reflex, the patient may, "in the course of a few days . . . be able to resume more normal bowel habits."[4]

Dosage: 3 Tablets t.i.d., each dose with a full glass of water, until normal stools pass regularly. Then reduce to minimum levels for as long as required. *To "wean" the cathartic addict,* ½ the usual laxative dose may be given together with Cellothyl for several days, then ¼ the usual dose, with Cellothyl, then Cellothyl alone. Daily fluid intake must be high.

1. *Bargen, J. A.: Gastroenterology 13:275, 1949.*
2. *Musick, V. H.: J. Oklahoma M. A. 43:360, 1950.*
3. *Schwcig, K.: New York State J. Med. 48:1822, 1948.*
4. *Council on Pharmacy and Chemistry: J.A.M.A. 143:897, 1950.*

Cellothyl®

brand of methylcellulose especially prepared by the Chilcott Process

available: Cellothyl Tablets (0.5 gram) in bottles of 50, 100, 500 and 5000.
Cellothyl Granules, for pediatric use, in bottles of 25 and 100 Grams.

Are you using the "7 Rules" for constipation correction?

CHILCOTT Laboratories DIVISION OF The Maltine Company
MORRIS PLAINS, NEW JERSEY

More Complete Therapy for Cough Control

Pyribenzamine® Expectorant

A Unique Combination of Non-narcotic Drugs

Anesthetic
Decongestant
Antispasmodic
Antihistaminic

FORMULA—Each teaspoonful (4 cc.) contains 30 mg. Pyribenzamine (tripelennamine) citrate, 10 mg. ephedrine sulfate, and 80 mg. ammonium chloride.

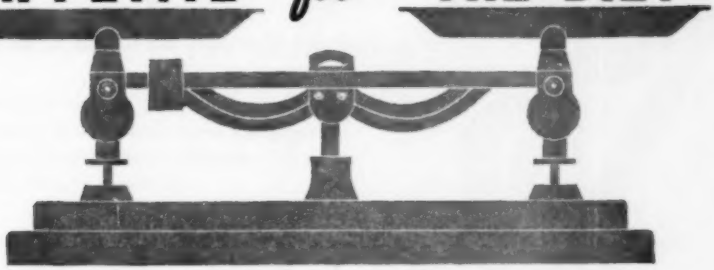
DOSAGE—Adults, 1 to 2 teaspoonfuls every 3 to 4 hours. Children, half the amount at same interval. Followed by full glass of water.

PYRIBENZAMINE
A NO. 1 ANTIHISTAMINIC

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

2/1853M

to make the **APPETITE** *fit* **THE DIET**



It is well known that the craving for food which besets many obese people cannot easily be controlled by the will alone. For them, adherence to a reducing diet often imposes a nervous strain, with consequent tension and irritability; and if they succumb to their urge to eat more, they have a sense of failure.

But appetite can now be modified by oral administration of 'Methedrine'. Then avoidance of over-eating becomes practically effortless, and the patient feels fitter and cheerful, as well as satisfied . . . with his meals and with his achievement.

Trials have shown that 'Methedrine' is a reliable anorexiant, and that it is effective in low dosage.

Literature describing dosage and recommended regimen will be sent on request.

REFERENCES:

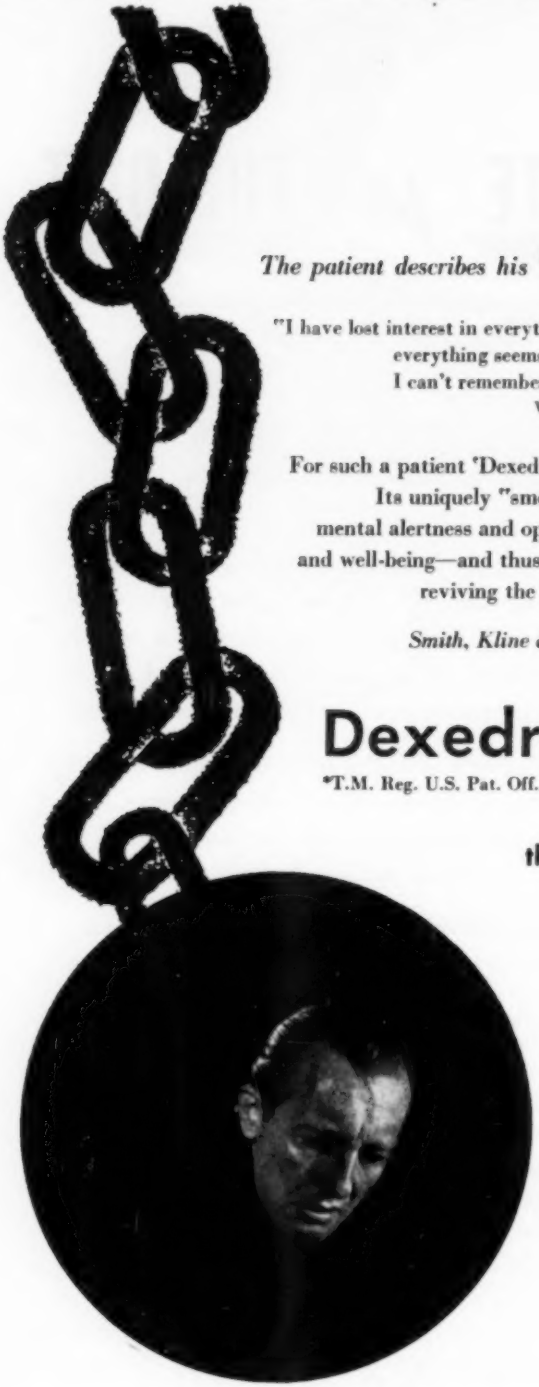
Ray, H. M.: Am. J. Digest. Dis., 14:153, 1947.
Shapiro, S.: ibid, 14:261, 1947.

'METHEDRINE'® brand

Methamphetamine Hydrochloride (d-Desoxyephedrine Hydrochloride)

Compressed products of 5 mg.—Scored to facilitate division.

BURROUGHS WELLCOME & CO., (U.S.A.) INC. TUCKAHOE 7, NEW YORK



The patient describes his **depression:**

"I have lost interest in everything—I have no ambition any more—
everything seems futile—I feel frustrated and lonely—
I can't remember or concentrate—I am *all slowed up.*"
Washburne, A.C.: Ann. Int. Med. 32:265, 1950.

For such a patient 'Dexedrine' Sulfate is of unequalled value. Its uniquely "smooth" antidepressant effect restores mental alertness and optimism, induces a feeling of energy and well-being—and thus has the happy effect of once again reviving the patient's interest in life and living.

Smith, Kline & French Laboratories, Philadelphia

Dexedrine* Sulfate

*T.M. Reg. U.S. Pat. Off.

the antidepressant of choice

tablets

elixir

In a ***critical evaluation***
of drugs for treating
urinary tract infections
it has been noted that:

SULAMYD®

(Sulfacetimide)

"combines the features of good antibacterial activity, low toxicity, and rapid renal elimination resulting in high urinary level. . . . Sulfacetimide . . . has the advantage of high solubility even in the physiological acid range of the urine, thereby minimizing almost to a negligible point the danger of concrement formation. . . ."[1] Because of its wide antibacterial range it may be preferable to penicillin and streptomycin.[2] It is well tolerated and remarkably free from side effects.[3]

DOSAGE: Therapeutic: 2 tablets t.i.d. for 10 days.
Prophylactic: 1 tablet t.i.d.

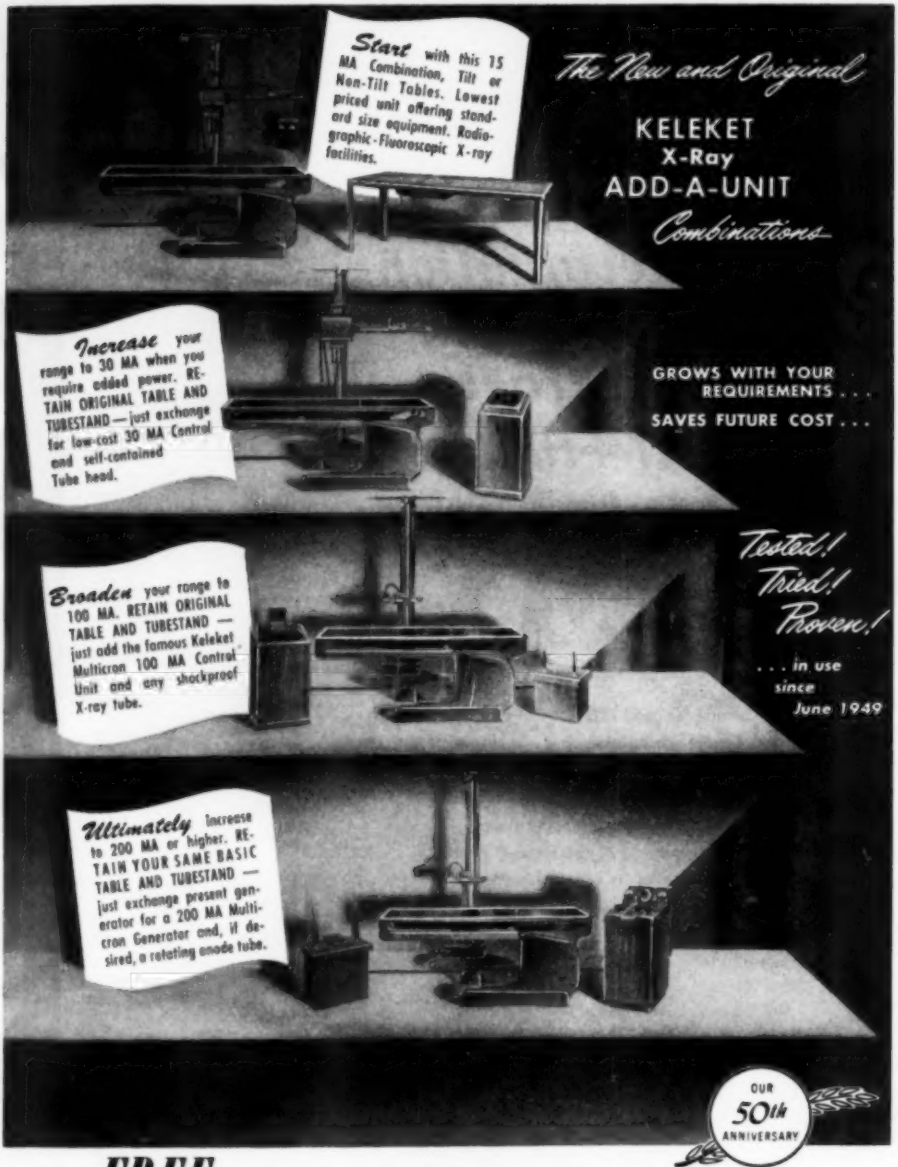
SULAMYD Tablets 0.5 Gm. in bottles of 100 and 1000 tablets.

1. Nesbit, R. M., and Glickman, S. L.: J. Michigan State M. Soc. 46:664, 1947.
2. Dodson, A. I.: West Virginia M.J. 45:1, 1949.
3. Seneca, H.; Henderson, E., and Harvey, M.: J. Urol. 61:105, 1949.

Schering CORPORATION · BLOOMFIELD, NEW JERSEY

SULAMYD

SCHERING


Start with this 15 MA Combination, Tilt or Non-Tilt Tables. Lowest priced unit offering standard size equipment. Radiographic-Fluoroscopic X-ray facilities.
The New and Original
KELEKET
X-Ray
ADD-A-UNIT
Combinations
Increase your range to 30 MA when you require added power. RETAIN ORIGINAL TABLE AND TUBESTAND — just exchange for low-cost 30 MA Control and self-contained Tube head.
GROWS WITH YOUR REQUIREMENTS . . .
SAVES FUTURE COST . . .
Broaden your range to 100 MA. RETAIN ORIGINAL TABLE AND TUBESTAND — just add the famous Keleket Multicron 100 MA Control Unit and any shockproof X-ray tube.
Tested! Tried! Proven!
. . . in use since June 1949
Ultimately Increase to 200 MA or higher. RETAIN YOUR SAME BASIC TABLE AND TUBESTAND — just exchange present generator for a 200 MA Multicron Generator and, if desired, a rotating anode tube.
OUR 50th ANNIVERSARY

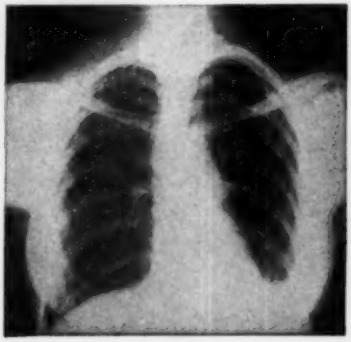
FREE: Write for *New* fully illustrated Brochure on the Keleket "Add-A-Unit Combinations."

The **KELLEY-KOETT** Manufacturing Co.
22111 WEST FOURTH ST. COVINGTON, KY.

The Oldest Original Name in X-Ray

Before Treatment (*9 days prior to Dihydrostreptomycin therapy*) *Diffuse lobular tuberculous pneumonia, lower half of left lung; thin-walled cavity above hilus (3 x 3.5 cm.).*

After 3 Mos. Treatment (*2 days after discontinuance of Dihydrostreptomycin*) *Considerable clearing of acute exudative process in the diseased lung; cavity smaller and wall thinner.*



Preferred Adjuvants in the treatment of

TUBERCULOSIS

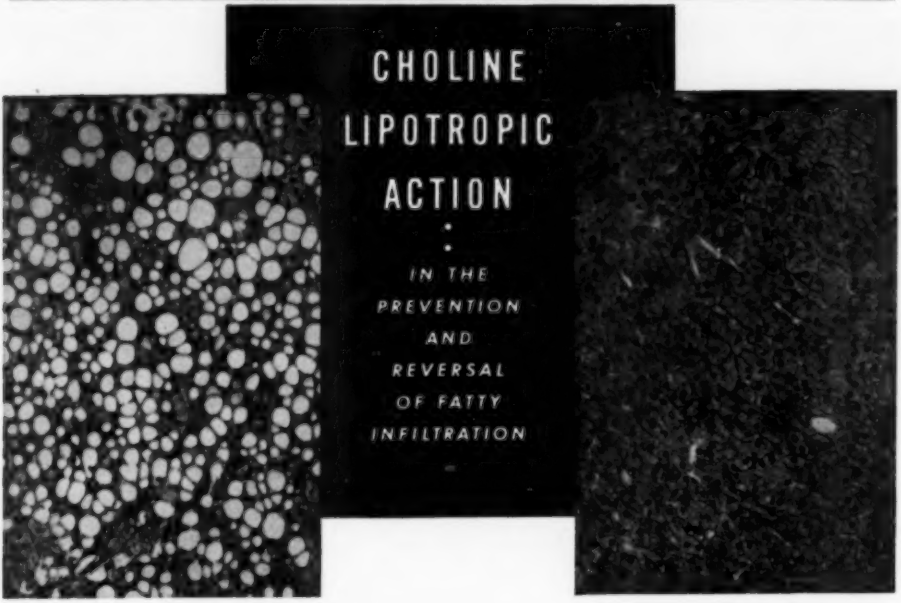
Dihydrostreptomycin and Streptomycin are unquestionably the most potent antibiotics now available for use against tuberculosis. Extensive clinical results have defined the important role of these antibiotics in suppressing the activity of the tubercle bacillus.

Detailed literature including indications, pharmacology, dosage, and administration is available upon request.

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

Streptomycin Calcium Chloride Complex Merck

Crystalline Dihydrostreptomycin Sulfate Merck



PATIENT . . . Middle aged female, with history and findings suggesting cirrhosis: loss of appetite, nausea, vomiting, vague gastrointestinal complaints, enlarged liver. Liver biopsy showed extensive fatty changes without fibrosis, indicating that the condition would be still amenable to treatment.

REGIMEN . . . High protein, high carbohydrate, moderate fat, reinforced with vitamin therapy and the lipotropic agent, *Choline (Flint)*. Patient remained ambulatory, except for short period of hospitalization required for biopsy.

RESULTS . . . At the end of four weeks' treatment, a second biopsy was taken, revealing an entire disappearance of the fatty changes. All signs and symptoms of hepatic failure had disappeared.

REMARKS . . . A successful end-result depends on early treatment of fatty infiltration during the prefibrotic stage—diagnosis at this time is governed largely by clinical signs and symptoms.

Choline (Flint) presents Choline Dihydrogen Citrate in two convenient dosage forms:

PALATABLE "SYRUP CHOLINE (FLINT)"
—one gram of choline dihydrogen citrate in each 4 cc.
Pint and gallon bottles.

CONVENIENT "CAPSULES CHOLINE (FLINT)"
—0.5 gram of choline dihydrogen citrate per capsule.
Bottles of 100, 500 and 1000.

FLINT, EATON & COMPANY
DECATUR, ILLINOIS

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

A

CARDIOTHERAPEUTIC GLYCOSIDAL

CONSTITUENT

OF DIGITALIS PURPUREA...

White's

GITALIGIN*

(ji-tal-i-jin)

—has been subjected to extensive clinical tests. Results in terms of margin of clinical safety and therapeutic efficacy have been so impressive that Batterman and co-workers report that Gitaligin is a ".....digitalis preparation of choice for the usual treatment of the patient with congestive heart failure."** Action is not as prolonged as that of digitoxin, but is more sustained than that of digoxin. Gitaligin is a cardioactive preparation which offers your patients *therapeutic* digitalis effect with an adequate margin of safety.

We shall be happy to forward literature and a trial supply of Gitaligin on request.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

WHITE LABORATORIES, INC., PHARMACEUTICAL MANUFACTURERS, NEWARK 7, N. J.

*"Gitaligin" Brand of gitalin (amorphous) is a trademark of White Laboratories, Inc

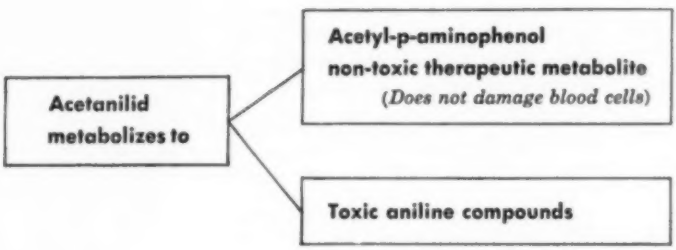
**Batterman, R. C.; De Graff, A. C., et al: Studies with Gitalin (amorphous) for Treatment of Patients with Congestive Heart Failure. Federation Proc. 9:256-257 (March) 1950.

Now offered to the medical profession for the first time

A new analgesic compound containing acetyl-p-aminophenol

. . . the non-toxic therapeutic metabolite of acetanilid

Long known as one of the most potent, rapid-acting analgesics, acetanilid has now been found to have a non-toxic therapeutic factor—*acetyl-p-aminophenol.* Studies at the Yale Laboratory of Applied Physiology and New York University School of Medicine show that *acetyl-p-aminophenol* has the high analgesic potency of acetanilid, without its toxicity. Unlike acetanilid and acetophenetidin compounds, *acetyl-p-aminophenol* does not damage blood cells, is safe even for chronic pain.



TRIGESIC

Squibb *acetyl-p-aminophenol*, Aspirin and Caffeine Tablets

Trigesic offers all the advantages of acetanilid . . . none of the disadvantages . . . plus the benefits of aspirin and caffeine

Each tablet contains 0.125 Gm. *acetyl-p-aminophenol;* 0.23 Gm. aspirin and 0.03 Gm. caffeine. *Bottles of 36, 100 and 1,000.* Also available as TRIGESIC WITH CODEINE, containing, in addition, 16 mg. codeine phosphate. *Bottles of 100.*

SQUIBB

"TRIGESIC" IS A TRADEMARK OF E. R. SQUIBB & SONS

ADVANCE *in antibiotic therapy*

for the first time this logical combination of antibiotics is available

Now, the combination of rapid-acting penicillin, repository penicillin and dihydrostreptomycin—in one convenient injection—places more effective therapy at the command of the physician. A broadened antibacterial spectrum gives greater coverage for more efficient and rapid control of many infections.

Penicillin S-R Trade Mark *with* Dihydrostreptomycin

Clinical Advantages of Penicillin S-R *with* Dihydrostreptomycin

- Effective against a wide range of gram-positive and gram-negative organisms
- Prompt effect on bacteria susceptible to penicillin or streptomycin alone
- "Crossfire" action on organisms susceptible to both antibiotics
- Synergistically increased antibiotic activity • Drug-fastness reduced

indications: Infections due to organisms susceptible to penicillin and/or dihydrostreptomycin.

preparation and administration: PENICILLIN S-R with DIHYDROSTREPTOMYCIN is easy to prepare and inject. It does not plug needles as small as 20 or 21 gage. To each single-dose vial aseptically add 3.3 cc. of: Water for Injection, U.S.P.; Physiological Sodium Chloride Solution, U.S.P.; or 5 per cent Dextrose Injection, U.S.P. Gently agitate to provide homogeneous suspension—solution for injection. A single dose (4 cc. prepared as directed) is injected intramuscularly, usually twice daily. Care must be taken to avoid intravenous injection, employing the usual precaution of aspiration.

Penicillin S-R *with* Dihydrostreptomycin

(Parke-Davis Penicillin and Dihydrostreptomycin Sulfate)

Each 4 cc. with aqueous diluent contains:

Crystalline procaine penicillin-G.....300,000 units
Crystalline sodium penicillin-G.....100,000 units
Dihydrostreptomycin (as the sulfate).....1.0 Gm.

DRAIN-FREE VIALS INSURE COMPLETE WITHDRAWAL OF CONTENTS

PARKE, DAVIS & COMPANY

MEDICAMENTA VERA

"TREATMENT *of* RHEUMATOID ARTHRITIS"

". . . . . .

There are still two main pillars of treatment of rheumatoid arthritis . . . . . .

The second chief preparation is gold salts, either alone or in combination with sulphur (AUROL-SULFIDE)."

(quoted from CLINICAL MEDICINE, August 1950, Vol. 57, No. 8, p. 159)

(underscorings ours)

Aurol-Sulfide combines to the highest degree the nontoxicity of colloidal gold with the therapeutic effectiveness of the gold salts in arthritis.

Aurol-Sulfide 2%, for parenteral use, contains 17.2 milligrams metallic gold, per cc. (15 cc, 30 cc, 60 cc vials)

Aurol-Sulfide 1%, for oral use. (½; 1; 4 fl. oz. bottles)

Please write for literature and clinical trials of Aurol-Sulfide

HILLE LABORATORIES
6007 N. Lincoln Avenue - CHICAGO 45

Please Mention this Journal when writing to Advertisers

the "magic"

of the coating . . .

another reason why Feosol Tablets

are the standard iron therapy

Feosol Tablets' specially developed coating insures *timed disintegration* of the tablet in the acid medium of the stomach and upper duodenum, where iron is best absorbed. Furthermore, each Feosol Tablet supplies 20 mg. blood-building iron per grain—*far more than ordinary iron preparations*. No wonder Feosol Tablets effect such rapid hemoglobin regeneration and prompt reticulocyte response in the iron-deficient patient.

'Feosol' T. M. Reg. U.S. Pat. Off.

Each Feosol Tablet contains 3 grains exsiccated ferrous sulfate, equivalent to approximately 5 grains crystalline ferrous sulfate.

Feosol Tablets

Smith, Kline & French Laboratories, Philadelphia

approved by
• NEW YORK CITY • CITY OF CHICAGO
• CANADIAN STANDARDS ASSN.

- Flow control panel permits temperature control within 1°F.
- Easily removable filter removes dust and pollen.
- All aluminum, corrosion-resistant construction.
- Hermetically sealed unit offers economical field adjustment, replacement.
- Complete Fiberglas insulation throughout.
- Baked enamel (pastel green) finish.

NOW-The O·E·M ICELESS MECHANAIRE

The First Tent Of Any Type Ever Accepted by Underwriters' Laboratories June 23, 1949

Here is another new contribution by O.E.M. to better oxygen therapy—the O.E.M. Mechanaire. This new iceless oxygen tent, first to be awarded the approval of the Underwriters' Laboratories, is a major contribution to the profession, offering features of safety, efficiency and economy never obtainable before.

Of major importance to users, the O.E.M. Mechanaire coil will not freeze up (ice) regardless of humidity or weather conditions. Perfectly balanced air conditioning prevents deposition of moisture on coil with consequent icing—permits instant, even thermostatic control of temperature, humidity. No defrosting is necessary.

The O.E.M. Mechanaire is also equipped with the *full-bed* O.E.M. Cleerlite Transparent Permanent Canopy (thickness, 5 mil). It is waterproof, will not pit or stipple in oxygen, is resistant to air, alcohol, acids—does not deteriorate or become brittle.

The O.E.M. Mechanaire is the lightest oxygen tent available today, weighing only 175 pounds. It handles easily with practically no effort.

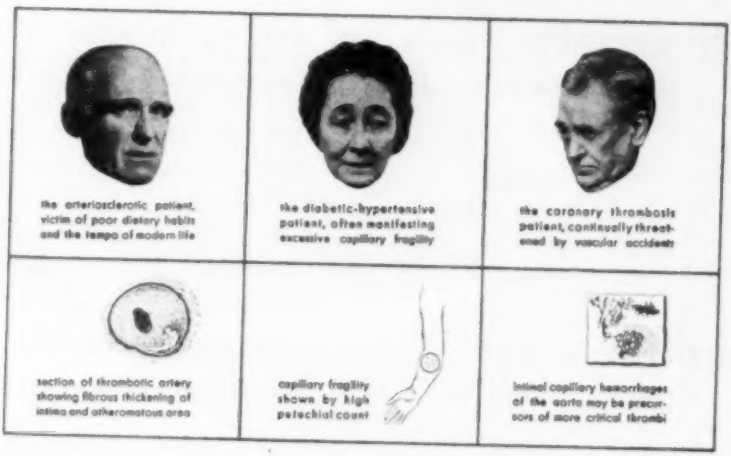
There are still other important features you should know about the O.E.M. Mechanaire. Write today for our new catalog.

O·E·M CORPORATION

(*Oxygen Equipment Mfg. Corp.*)
FITCH ST., EAST NORWALK, CONN.

POTENT PROTECTION

> > > against the combined threats of arteriosclerosis and capillary fragility


the arteriosclerotic patient, victim of poor dietary habits and the tempo of modern life
the diabetic-hypertensive patient, often manifesting excessive capillary fragility
the coronary thrombosis patient, continually threatened by vascular accidents
section of thrombotic artery showing fibrous thickening of intima and atheromatous area
capillary fragility shown by high petechial count
intimal capillary hemorrhages of the aorta may be precursors of more critical thrombi

VASCUTUM

TRADEMARK

for the life that begins at forty

VASCUTUM* makes possible a dual attack, both prophylactic *and* therapeutic, in the two-front battle against hypercholesterolemia and capillary fragility, combining in one medication:

1 Potent amounts of lipotropic agents, to promote decholesterolization in atherosclerosis, liver cirrhosis and diabetes mellitus.

2 Therapeutic amounts of rutin and ascorbic acid, to combat related capillary weakness effectively. Damaging retinal hemorrhage often results from excessive capillary fragility and associated abnormal cholesterol deposits.

The average daily dose (6 tablets) provides:

Choline	1 Gm.	Pyridoxine HCl	4 mg.
Inositol	1 Gm.	Rutin	150 mg.
dl-Methionine	500 mg.	Ascorbic Acid	75 mg.

VASCUTUM marks a distinct advance in the management of interrelated degenerative diseases affecting the middle-aged and elderly.

SUPPLIED in bottles containing 100 tablets.

SCHENLEY LABORATORIES, INC.
350 FIFTH AVENUE • NEW YORK 1

© Schenley Laboratories, Inc.

*The word VASCUTUM is a trademark of Schenley Laboratories Inc.

3 Useful Cardiac Drugs

❶ Thesodate — Brewer IN ANGINA PECTORIS

(Theobromine Sodium Acetate 7½ gr. enteric coated)

Thesodate has been proven effective in increasing the capacity for work in individuals suffering from coronary artery disease. One Thesodate tablet four times a day (after meals and at bedtime) helps to maintain improved heart action and increased coronary artery circulation.

❷ Enkide — Brewer IN LUETIC HEART DISEASE

(Potassium Iodide one gram or half gram enteric coated)

Enkide is useful as an adjuvant in tertiary syphilis and wherever potassium iodide therapy is indicated. Enkide insures accuracy of dosage, absence of gastric irritation and convenience of administration. Patients are more apt to follow prescription directions because of these advantages.

❸ Amchlor — Brewer IN CARDIAC EDEMA

(Ammonium Chloride one gram enteric coated)

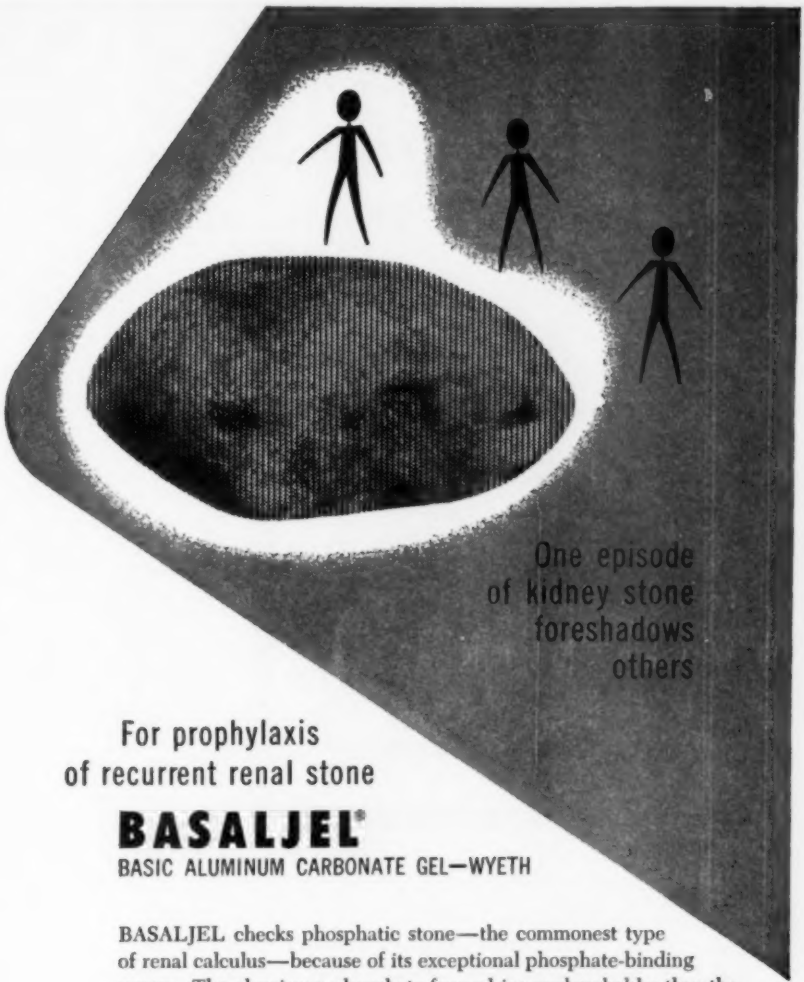
Amchlor cuts in half the number of tablets each patient takes when large amounts of ammonium chloride are prescribed. This convenience to the patient helps to insure full and complete use of the entire amount prescribed. Amchlor is useful in cardiac edema, hypertension, dysmenorrhea, Meniere's Syndrome, etc.

Samples and Literature Available Upon Request.

Brewer EST. 1852

BREWER & COMPANY, INC.

WORCESTER 8, MASSACHUSETTS U.S.A.



For prophylaxis
of recurrent renal stone

BASALJEL®

BASIC ALUMINUM CARBONATE GEL—WYETH

BASALJEL checks phosphatic stone—the commonest type of renal calculus—because of its exceptional phosphate-binding power. The aluminum phosphate formed is nonabsorbable; thus the phosphate is eliminated in the feces, not in the urine.

BASALJEL is Safe in doses needed for full effect. Basaljel is palatable.

BASALJEL is clinically established as a valuable safeguard against renal calculi after surgery or prolonged immobilization.

Low Phosphorus Diet Sheets, for use by your patients, will be sent to you upon request.

Wyeth Incorporated • Philadelphia 3, Pa. Wyeth®

The Picture Framed in the Minds of Physicians

Comprise the entire properties of the leaf of Digitalis

Physiologically Standardized

Therefore always Dependable

Each Pill is equivalent to one U.S.P. Digitalis Unit

Clinical samples sent to physicians on request

Davies, Rose & Company, Limited
Boston 18, Massachusetts

D 22

THE *Cardi-all*

BY

BECK-LEE

world's largest exclusive manufacturer of electrocardiographs.

A TRULY OUTSTANDING INSTRUMENT!

THE Cardi-all, direct writing electrocardiograph, provides records of highest fidelity through the full frequency Galvomotor galvanometer. The physician is assured of clinically precise cardiograms.

Operation of the instrument has been simplified by the introduction of automatic protection devices. Manual protection of the instrument is no longer necessary and anyone can be trained in the operation of the Cardi-all in less than one hour.

Paper loading requires only 10 seconds and the new welded bridge type stylus virtually eliminates stylus replacement.

THE CARDI-ALL, complete with all accessories is . . . **$495**

The Cardi-all, measuring 8½ x 11 x 14¼ inches weighs only 27 pounds completely loaded and all accessories are carried *within* the instrument. Effective voltage stabilization, automatic grounding and the special AC control permit the use of the instrument, with equal ease, in the office, home or hospital.

BECK-LEE CORPORATION

630 W. JACKSON BLVD. • CHICAGO 6, ILLINOIS

QUARTZ STRING ELECTROCARDIOGRAPHS

MODEL E . . . $645 **MODEL ERA . $725**

Accepted for advertising in the Journal of the AMERICAN MEDICAL ASS'N

When low-sodium dieters complain their food tastes like hay...

Diasal is a new, improved type of salt substitute. It has the crystalline look of salt—virtually *duplicates the taste of salt! Diasal* gives a real salty flavor to flat-tasting, salt-free diet foods. It enables bored dieters to keep on with their diets—*promotes patient cooperation. Contains no lithium.*

Diasal is used just like salt, at the table and in cooking.

Constituents: potassium chloride, glutamic acid and inert excipients combined to stimulate food flavors, without bitterness or after-taste. Diasal may be freely prescribed as a diet adjunct in conditions of congestive heart failure, hypertension, arteriosclerosis and edemas of pregnancy.

Available in 2 oz. shakers and 8 oz. bottles.

DIASAL®

restores flavor and taste

no sodium · no lithium

For SAMPLE SHAKERS and low-sodium DIET SHEETS for several patients, write E. Fougera & Co. Inc. 75 Varick St., New York 13, N. Y.

Canadian Distributors: Rougier Freres, Montreal

Mr. De-Ouncer

is a Vitamin Bouncer

●Feast then famine—so goes his battle of the bulge. For him, and other subclinical vitamin deficients, why not supplement their new dietary regime with DAYAMIN? These potent and appealing capsules encourage dietary adherence, make sure that patients get the vitamins they need (see formula). Prescribe one daily as a supplement, more for therapeutic purposes. In bottles of 30, 100 and 250. Tasty DAYAMIN Liquid is readily accepted by patients who can't or won't take capsules. The Liquid is supplied in bottles of 90 cc., 8 fluidounces and 1 pint.

Abbott

specify **Dayamin®**

(Abbott's Multiple Vitamins)

NOTE THE FORMULA

Each Dayamin Capsule contains:

Vitamin A	10,000 U.S.P. units
Vitamin D	1000 U.S.P. units
Thiamine Hydrochloride	5 mg.
Riboflavin	5 mg.
Nicotinamide	25 mg.
Pyridoxine Hydrochloride	1.5 mg.
Pantothenic Acid (as calcium pantothenate)	5 mg.
Ascorbic Acid	100 mg.

Ventral Hernia

A GREATER LIABILITY OF THE OBESE

● Photograph of patient, 51 years old. Weight — 226 lbs.; height — 5 ft. 5 in.

Patient was operated four years ago for fibroid tumors of the uterus when weighing 240 lbs. Complete disruption of the wound occurred on the fourth day. Pneumonia followed, requiring a six month's stay in the hospital.

● Photograph of patient after application of support.

The support holds the abdomen and its contents up and back, thus relieving the drag on the lumbar fascia and placing the load upon the pelvic girdle.

The gluteal region is well supported, thus relieving the pull on the posterior portion of the crests of the ilia.

The chief characteristic of Camp Supports is their ability to steady and support the pelvic girdle. It is from this support of the bony pelvis that the exceptional support of the abdomen and back takes place, as noted in the above illustrations.

CAMP *Supports*

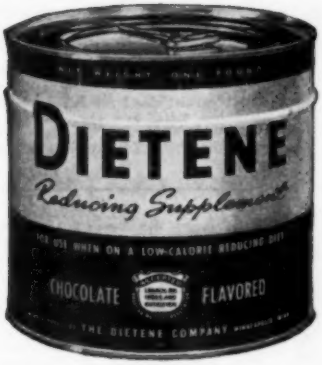
S. H. CAMP and COMPANY • JACKSON, MICHIGAN

World's Largest Manufacturers of Scientific Supports

Offices at: 200 Madison Ave., New York; Merchandise Mart, Chicago; Windsor, Ont.; London, Eng.

FREE TO PHYSICIANS...

New Low-Sodium Reducing Diets



A supply of sodium-restricted, 1000-calorie diets free of advertising and made to look as if they were typed in your office will be sent to you on your request.

The value of sodium-restricted diets in congestive heart failure, high blood pressure, and certain forms of renal disease has been established by numerous clinical studies. In patients requiring a reduction of weight with a sodium-restricted diet, specification of **DIETENE®** provides a truly palatable means of accomplishing the desired result *without sacrificing nutritional adequacy, or jeopardizing the low-sodium regimen.*

DIETENE is an excellent low-calorie source of biologically superior proteins plus protective amounts of essential vitamins and minerals.

SUPPLIED: In 1-lb. cans, plain or chocolate flavor, available through all pharmacies at $1.55.
PATIENTS ENJOY TAKING DIETENE.

SEND FOR YOUR FREE SUPPLY OF 1000-CALORIE, LOW-SODIUM DIETS TODAY BY MAILING THE ATTACHED COUPON.

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

Not advertised to the laity

THE DIETENE COMPANY DI 110
518 FIFTH AVENUE SOUTH, MINNEAPOLIS 15, MINNESOTA

Please send me a free supply of the new 1000-calorie DIETENE Reducing Diet, providing only 0.7 to 1 Gm. of sodium per day.

Name.....**M.D.**
(Please Print)

Address.....

City.....**Zone**.....**State**.....

Why the Viso Cardiette is still today's leading electrocardiograph!

Sanborn Company has been designing and making Ecgs for over 26 years (9 models since 1924; over 15,000 Cardiettes, both photographic and direct writing, since 1935) and has thereby gained a thorough knowledge of both the clinical advantages and shortcomings of every type of Ecg that has been, and is being used. Thus, Sanborn Company *knows how* to make an Ecg that has *all* the advantages every modern doctor wants. The more outstanding of these are listed below, together with indisputable facts which point to Viso *leadership*.

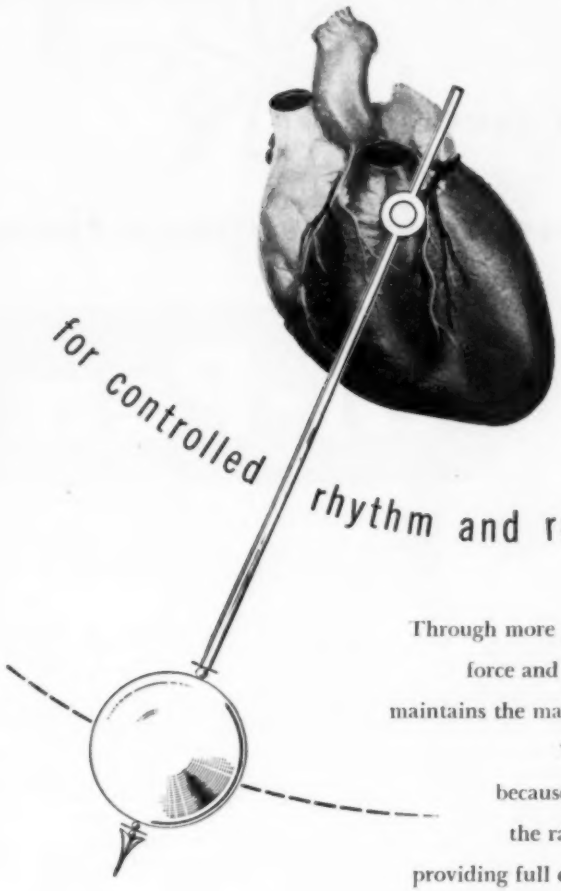
Top-quality, "well dressed" distinctive design . . . a professional appearance that's in keeping with the nature and value of the instrument's purpose . . . complete instrument contained in a selected mahogany case, total weight including accessories in cover 33 lbs . . .	**Note similarity in compactness and appearance of other "direct writing" 'cardiographs introduced *long after* the Viso's design was "accepted"!**
. . . a swift, simple operating technic that *anybody* can quickly learn . . . only two controls needed for routine testing, one of which selects *all* leads without need to shift electrode connections . . .	**"Instomatic" lead selection was a Sanborn "first" *over ten years ago*. Also, the Viso was the first to eliminate "AC" without a separate ground.**
. . . standard appearing 'cardiograms with ribbon-type baseline, and in *true rectangular co-ordinates* . . . no ink required . . . recordings made on plastic coated "Permapaper" by heated stylus . . .	**The Viso was the first direct writing 'cardiograph to *eliminate arc writing* . . . and the first to use *plastic-coated* record paper.**
. . . dependable, sturdy construction guarantees long, continuous service and economy of maintenance . . . three separate components, connected electrically and mechanically, may be lifted as single unit from case . . .	**The value of "unitized" construction was apparent to Sanborn engineers *ten years ago*, and is now incorporated by other makers!**
. . . accurate, undistorted records. The Viso not only meets, but in most cases *exceeds* standard ECG performance requirements . . . rigid factory tests on *each* instrument assures peak performance, year after year . . . almost no maintenance required . . .	**The original Viso, model 572, was the *first* 'cardiograph ever to be Accepted by the AMA Council on Physical Medicine, May, 1948!**

The leadership attained by Sanborn Company's years of experience is conducive to the confidence in the maker that you like to feel when making such an important addition to your practice as a Viso-Cardiette.

For descriptive literature, write to Dept. IM

SANBORN COMPANY

CAMBRIDGE 39, MASSACHUSETTS



for controlled rhythm and rate . . .

Through more precise control of contractile force and rhythm, Digitaline Nativelle maintains the maximum efficiency obtainable. *This maintenance is positive* because *absorption is complete* and the rate of *dissipation is uniform;* providing full digitalis effect between doses. All, with virtual freedom from untoward side effects.

Digitaline Nativelle

Chief active principle* of digitalis purpurea (digitoxin)

**Not an adventitious mixture of glycosides*

Send for new brochure . . . "Modern Digitalis Therapy," Varick Pharmacal Co., Inc. (Div. of E. Fougera & Co., Inc.) 75 Varick St., New York, N.Y.

MAINTENANCE: 0.1 or 0.2 mg. daily depending upon patient's response.
CHANGE-OVER: 0.1 or 0.2 mg. of Digitaline Nativelle replaces 0.1 gm. or 0.2 gm. whole leaf.
RAPID DIGITALIZATION: 0.6 mg. initially, followed by 0.2 or 0.4 mg. every 3 hours until patient is digitalized.

All you need in a Penicillin Preparation

Bi-Pen

Procaine Penicillin and
Buffered Crystalline Penicillin
For Aqueous Injection

RAPID ABSORPTION

The 100,000 units of crystalline penicillin G potassium in each dose of Bi-Pen is rapidly absorbed, leading to a significant, initially high plasma penicillin level. Thus, in the initial stages of therapy, the specific action of penicillin is made available immediately.

PROLONGED LEVELS

Slower absorption of the crystalline procaine penicillin G (300,000 units per dose) produces detectable levels for at least 24 hours following each injection. Once-a-day administration usually suffices.

EASILY PREPARED

The addition of Water for Injection U.S.P. is all that is necessary to prepare Bi-Pen for injection. The insoluble procaine penicillin salt goes into suspension readily, forming a well dispersed, homogeneous mixture.

READILY INJECTED

Bi-Pen is free-flowing and is readily aspirated into the syringe and injected into the tissues. It should be given intramuscularly only. Average dose, 1 cc. (400,000 units) daily, but this quantity may be doubled if indicated.

Bi-Pen is supplied in three package sizes: (1), 5 dose rubber-capped vials containing two million units, (2), single dose vials (400,000 units) packaged singly, and (3), single dose vials in boxes of 50.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION, 17 EAST 42ND STREET, NEW YORK 17, NEW YORK

5 REASONS WHY

the **BAXTER Closed System** is an established, ***preferred*** method of blood banking...

no contact with outside air

With the BAXTER CLOSED SYSTEM, blood can be drawn and stored for a maximum period; or, plasma or serum can be prepared—all without risk of contamination from outside air.

controlled vacuum

BAXTER containers utilize mechanically induced vacuum to draw a large volume of blood into the bottle. This vacuum permits transfer of blood or plasma from one container to another, aseptically, without any break in the closed technique.

steady flow

During administration air enters the container through an air tube. A steady flow of blood or solutions results, rather than intermittent gurgling.

faster and easier

The BAXTER method is a model of streamlined efficiency, simplicity, and safety, and can be brought into use instantly.

standardized technique

Because the BAXTER closed system is used in more hospitals than any other method, most nurses are thoroughly trained in the procedure.

***a demonstration** of the complete BAXTER program of blood banking and parenteral therapy can be arranged without obligation.*

Manufactured by
BAXTER LABORATORIES, INC.
Morton Grove, Illinois • Cleveland, Mississippi

Produced and distributed in the 11 western states by DON BAXTER, INC., Glendale, California

DISTRIBUTED AND AVAILABLE IN THE 37 STATES EAST OF THE ROCKIES (except in the city of El Paso, Texas) THROUGH
AMERICAN HOSPITAL SUPPLY CORPORATION
GENERAL OFFICES • EVANSTON, ILLINOIS

can
we
believe
our
census?

Yes, the fact is that a bacterial census following therapeutic doses of SULFASUXIDINE® succinylsulfathiazole will show a rapid reduction of *E. coli* organisms from 10,000,000 to less than 1,000 per gram of wet stool.

Sulfasuxidine

succinylsulfathiazole

SHARP & DOHME

SULFASUXIDINE is specifically indicated as a safeguard against peritonitis before and after intestinal surgery, and is particularly valuable prophylactically in radical procedures.[1] It has also proved effective for control of ulcerative colitis and *E. coli* infections of the genitourinary tract,[2] and is considered a drug of choice in treatment of acute or chronic bacillary dysentery, including carrier states of this disease.[3] Toxic reactions are negligible, since 95% of the dose remains in the gastrointestinal tract.
Supplied in 0.5-Gm. tablets, bottles of 100, 500, and 1,000; powder in ¼ and 1 lb. bottles.
Sharp & Dohme, Philadelphia 1, Pa.

1. Internat. Abstr. Surg. *83*:1, July 1946.
2. Am. J. Obst. & Gynec. *49*:114, Jan. 1945.
3. J.A.M.A. *128*:1152, Aug. 18, 1945.

ANNALS OF
INTERNAL MEDICINE

VOLUME 33 NOVEMBER, 1950 NUMBER 5

EFFECTS OF ADRENOCORTICOTROPIC HORMONE IN PNEUMONIA: CLINICAL, BACTERIOLOGICAL AND SEROLOGICAL STUDIES *

By EDWARD H. KASS,† PH.D., M.D., SIDNEY H. INGBAR, M.D., and MAXWELL FINLAND, M.D., F.A.C.P., *Boston, Massachusetts*

ALTHOUGH adrenal cortical and pituitary adrenocorticotropic hormones have produced remarkable alterations in the course of many clinical disorders,[5, 9] the mechanisms by which these changes are induced remain obscure. Immunologic factors have been considered to play an important rôle in the pathogenesis of, or recovery from, many of the diseases in which cortisone and ACTH have exerted apparently beneficial effects. Because adrenal hormones have been implicated in immunologic processes,[9, 10] attempts have been made to explain the effects of cortisone and ACTH in terms of immunologic mechanisms. However, it is obviously difficult to study the effects of ACTH on immunologic mechanisms in such diseases as rheumatic fever, rheumatoid arthritis, and the collagen diseases, in which the etiology is so poorly understood, even though some of the more striking beneficial effects have been reported in these diseases.

It appeared desirable, therefore, to study the effects of ACTH and adrenocortical hormones on infectious diseases in which the etiology, pathogenesis, and mechanisms of resistance are better understood. Such a study would also offer the opportunity to reinvestigate some of the aspects of immunity and resistance to infection which have received relatively little attention since the advent of antibiotic therapy.

This report is concerned with the effects of ACTH ‡ on the clinical manifestations, bacteriologic flora and serologic responses of three patients with pneumococcal and two with primary atypical (viral) pneumonia.

* Received for publication July 7, 1950.
From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.
Aided by a grant from the United States Public Health Service.
† Senior Fellow in Virus Diseases, National Research Council.
‡ Furnished by Dr. John R. Mote, of the Armour Laboratories.

Copyright, 1950, by The American College of Physicians

Case Reports

Case 1 * (figure 1). A 16 year old schoolboy entered the Boston City Hospital a few hours after the sudden onset of severe pain in the left side of the chest, followed by a shaking chill. He had had an upper respiratory illness for one week prior to admission, with a cough productive of whitish sputum which became brown in color two days before entry. The patient had had pneumonia two years previously and had made an uneventful recovery. The past and family histories were otherwise not contributory.

At entry the patient appeared hot, flushed, and acutely ill. The temperature was 104.6° F., pulse 130, respirations 28, and blood pressure 110/70 mm. Hg. He

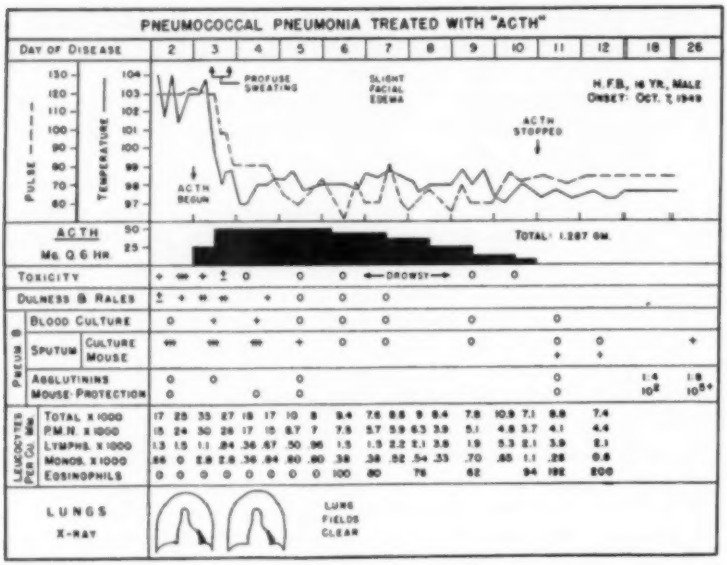


FIG. 1.

coughed infrequently and raised small amounts of gray, mucopurulent sputum. Examination of the eyes, ears, nose, and throat was negative save for slight pharyngeal injection. Slight dullness and scattered fine moist râles were found over the base of the left lung posteriorly, with no change in vocal fremitus or breath sounds. The remainder of the physical examination was not remarkable.

Laboratory work at entry revealed 14.5 gm. of hemoglobin per 100 ml. of blood and 16,500 leukocytes per cu. mm., with 88 per cent polymorphonuclear leukocytes, 8 per cent lymphocytes, and 4 per cent monocytes. No eosinophiles were found by absolute count.[5] The urine and feces were not remarkable, the Hinton test was negative, and the blood urea nitrogen was 11 mg. per 100 ml.

The sputum was gray and tenacious, and contained many polymorphonuclear

* Some of the findings in Case 1 and Case 4 have been presented in a preliminary report elsewhere.[3]

leukocytes and an average of 156 type 8 pneumococci per high dry field. The initial blood culture was sterile.

The patient was observed without specific treatment for eight hours. During this time he received 0.6 gm. acetylsalicylic acid, and 1500 ml. of physiologic saline. His temperature fluctuated between 101.4 and 104.2° F., the pulse remained at 120, and the respirations rose to 36. After hydration, the hematocrit was 43 per cent, the hemoglobin 12.5 gm., but the white blood cell count rose to 25,000, with 94 per cent polymorphonuclear leukocytes. There were no eosinophiles. ACTH was then administered intramuscularly every six hours; two doses of 25 mg. were followed by 50 mg. doses for 72 hours, after which the daily dose was gradually diminished until the drug was withdrawn. A total of about 1.3 gm. was given over a period of eight days.

At the time of the second dose the patient was still acutely ill, his temperature was 103.6°, pulse 128, respirations 28, and leukocyte count 35,000. There was no change in the clinical appearance, pleuritic pain, or physical findings. The appearance of the sputum was unchanged grossly and microscopically. Within the next 12 hours, however, there was profuse diaphoresis, the temperature fell to 98° F., the pulse fell to 80, and the respirations to 20. The sputum at this time became rusty and was still loaded with type 8 pneumococci. The organisms stained evenly, with no evidence of loss of viability or of phagocytosis. The patient felt much improved, began to eat, had no more chest pain, coughed only rarely, and was asymptomatic. However, a blood culture taken at this time was positive for type 8 pneumococci, and the leukocyte count was still 27,800. On the following day, the chest was virtually clear by physical signs and by roentgen-ray, and the patient was eager to leave the hospital. However, the sputum still contained an average of 54 pneumococci per high dry field, and there were many polymorphonuclear leukocytes. The hematocrit at this time was 35 and the leukocyte count 18,000. A second blood culture, taken 36 hours after the first dose of ACTH and 24 hours after the temperature had reached normal, was again positive for type 8 pneumococci.

Repeated blood cultures after this time were negative. Sputum was no longer available by the third day of administration of ACTH, but throat cultures yielded type 8 pneumococci. Later, pneumococci could be demonstrated only after mouse inoculation of throat cultures, but they were still present as late as 26 days after the onset of the illness. The patient remained afebrile and asymptomatic, with normal leukocyte counts after the third day of treatment with ACTH, and his eosinophile counts and hematocrit slowly returned to normal values as the dose of ACTH was diminished. The patient's highest weight, while he was on ACTH therapy, was 138 lb., and after withdrawal of ACTH his weight fell to 133 lb.

Agglutinins and mouse protective antibodies for the homologous pneumococci were still absent on the eleventh day after the onset of the illness, but they were demonstrated in significant titers on the eighteenth day and subsequently increased in titer.

The outstanding features of this case are (1) the rapid defervescence following the institution of therapy with ACTH; (2) the prompt relief of symptoms; (3) the disappearance of evidence of toxemia; (4) the appearance of bacteremia at the time of the induced crisis and its persistence at a time when the patient was afebrile and free of symptoms; (5) the persistence of pneumococci in the sputum and throat cultures for at least 28 days after the crisis; (6) the development of specific antibodies at the usual time, and (7) the failure of the lesion to extend, and its rapid resolution during treat-

ment. The significance of the latter findings is difficult to evaluate in a young, previously healthy patient in whom the prognosis for recovery is very good even in the absence of therapy. However, the failure of the consolidation to extend, and its rapid clearing after therapy with ACTH, could hardly have been expected to occur spontaneously.

Several additional effects, presumably due to ACTH, were noted. The patient became glycosuric, although his blood sugar levels and glucose tolerance curves were not abnormal. This apparent renal glycosuria has been reported separately and its significance discussed.[7] Suffice it to say that this effect suggests that ACTH may induce significant changes in renal function. The considerable retention of water, as demonstrated by the gain in weight and drop in hematocrit, was accompanied by slight facial edema which appeared on the fifth day after ACTH was begun. Bradycardia developed during the time when ACTH was being administered and disappeared when the ACTH was stopped. There were no significant changes in blood pressure during the course of the illness.

Case 2. A 41 year old Negro truck driver entered the Boston City Hospital 24 hours after the sudden onset of shaking chills accompanied by feverishness, frontal headache, pleuritic pains, and rusty sputum. He had had a mild upper respiratory tract infection with a slight cough productive of scanty gray-white sputum during the preceding week.

At entry the patient was acutely ill with a temperature of 103° F., pulse 96, respirations 28, and blood pressure 110/76 mm. Hg. There were rapid, grunting respirations, and the right side of the chest was splinted. There was slight dullness limited to the right base posteriorly. Vocal fremitus was slightly increased over the area of dullness, with bronchovesicular breathing and crepitant râles heard over the same area. Whispered pectoriloquy and friction rub were absent. The remainder of the physical examination was noncontributory.

Laboratory studies revealed a hemoglobin of 13.2 gm., hematocrit of 46 per cent, 5.6 million erythrocytes per cu. mm., and 15,300 leukocytes, of which 84 per cent were polymorphonuclear. There were no eosinophiles by absolute count. The urine and blood urea nitrogen were within normal limits, and the Hinton test was negative. The sputum was rusty, tenacious, and contained an average of four type 2 pneumococci per high power field, as well as many polymorphonuclear leukocytes. Two initial blood cultures showed no growth. A roentgen-ray film of the chest at entry showed a fan shaped area of consolidation radiating peripherally from the hilum and involving about two-thirds of the right lower and middle lobes.

The patient was observed without specific therapy for 12 hours, during which time his temperature changed very little but his pulse rose to 120 and his respirations to 36. Consolidation of the lungs had proceeded peripherally by roentgen-ray and by physical examination, and there was now well-developed dullness over the right base and in the right axilla, with bronchial breathing, whispered pectoriloquy, egophony and crepitant râles over the entire right lower and middle lobe areas. The chest film now showed complete consolidation of the right lower and middle lobes. The sputum was still rusty and contained an average of 20 pneumococci per high power field. Several blood cultures taken at this time were negative.

Twelve hours after entry the patient received 12.5 mg. ACTH intramuscularly, and this was repeated six hours later. During the initial 12 hours after the hormone was first administered, the patient's condition seemed somewhat worse. His tem-

perature rose to 104° F., pulse to 128, and respirations to 40, and he was fatigued, drowsy and breathing laboriously. At six hour intervals for the next 72 hours the patient was given 25 mg. ACTH. The dose was reduced successively to 75, 50 and 25 mg. per day (in four doses) during the next three days. Within two hours after the third dose, the temperature, pulse and respiratory rate began to fall and there was marked diaphoresis. Within 24 hours after the onset of treatment the temperature, pulse and respiration were within normal limits, and the patient was obviously much improved. He was free of pleuritic pain, coughed infrequently, and had an excellent appetite. The physical signs in the chest were unchanged, and the sputum was still rusty and contained many polymorphonuclear leukocytes and 26 pneumococci in each microscopic field. Repeated blood cultures were taken during the course of the illness, but only one, taken three hours after the first dose of ACTH, was positive.

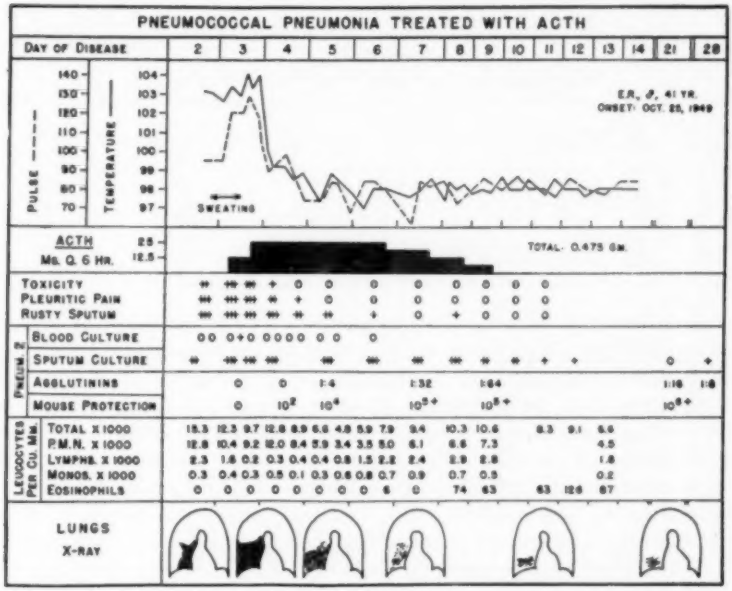


FIG. 2.

The relevant features of the clinical course and laboratory findings in this case are shown in figure 2 and table 1. The patient remained afebrile and asymptomatic and had an uneventful recovery, with clearing of the consolidation by physical signs and by roentgen-ray, save for slight residual atelectasis in the right middle lobe. However, the sputum continued to be rusty until the eighth day, and viable, unphagocytosed type 2 pneumococci were present in abundance for 10 days, after which sputum was no longer available. Throat cultures on the eleventh and twelfth days were positive for pneumococci, but they could not be demonstrated on subsequent cultures directly. However, on the twenty-eighth day type 2 pneumococci were again demonstrated, but this time they were found only after mouse inoculation of the broth culture of the throat swabbings. Leukocytosis did not return after ACTH was with-

drawn, and eosinophiles, which were absent during the acute illness, returned slowly as the dose of ACTH was decreased.

Antibodies were absent until the fourth day of illness (the second day of treatment), at which time mouse protective antibodies appeared and were followed, on the next day, by the appearance of agglutinins. This patient, like the preceding one, had transient bradycardia while he was receiving ACTH, but his blood pressure did not change significantly during the entire course of illness. Although the hematocrit dropped during the course of administration of the hormone, there was no significant change in weight.

One month after discharge the patient developed a mild upper respiratory tract infection. A throat culture at this time revealed a few type 2 pneumococci, but antibiotic therapy was withheld and the patient made an uneventful and rapid recovery with no loss of time from his work. His chest remained clear by physical examination and by roentgen-ray during the latter illness.

TABLE I

Body Weight and Additional Blood Findings in Case 2

Day of Illness	Hemoglobin grams per ml.	Hematocrit %	Erythrocytes per cu. mm.	Sedimentation Rate (Corrected) mm. per hr.	Weight lb.
2	13.7	46	5.6	30	154
4		42.5	4.13	42	154
6	13.0	39	4.16	42	153
8	13.5	41	4.3	28	151
13	13.5	42	4.4	26	154

The noteworthy features of this case are (1) the induction of a crisis following the administration of ACTH to a patient who had a rapidly advancing lobar pneumonia with bacteremia and consolidation of two lobes of the right lung; (2) the persistence of rusty sputum for six days after the crisis; (3) the persistence of pneumococci in the throat for at least one month after the crisis; (4) absence of evidence of increased phagocytosis of pneumococci, or bactericidal activity in the sputum; (5) early appearance of antibodies during ACTH administration; (6) the resolution of the pneumonia, which appeared to be neither accelerated nor delayed, and (7) failure of ACTH to affect the sedimentation rate significantly despite the rapid and favorable clinical response.

Case 3 (figure 3). A 48 year old white male clerk entered the Boston City Hospital complaining of cough, nausea, vomiting, severe pleuritic pain, fever, and shaking chills for two or three days. He had been on an alcoholic spree for the nine days preceding the onset of illness and had consumed one to three pints of whiskey daily. Two years previously he had had pneumonia following a similar alcoholic episode. The past, family and social histories were otherwise noncontributory.

The patient was a well nourished male and when first seen he appeared acutely ill, with grunting, shallow, rapid respirations and a frequent, hacking, painful cough. The temperature was 103° F., pulse 108, respirations 30, and blood pressure 130/80 mm. Hg. The skin was hot, dry and free of stigmata of cirrhosis. The eyes, ears, and nose were not remarkable, but the mucous membranes of the oropharynx were moderately injected and the uvula was diffusely reddened and edematous. No exudate

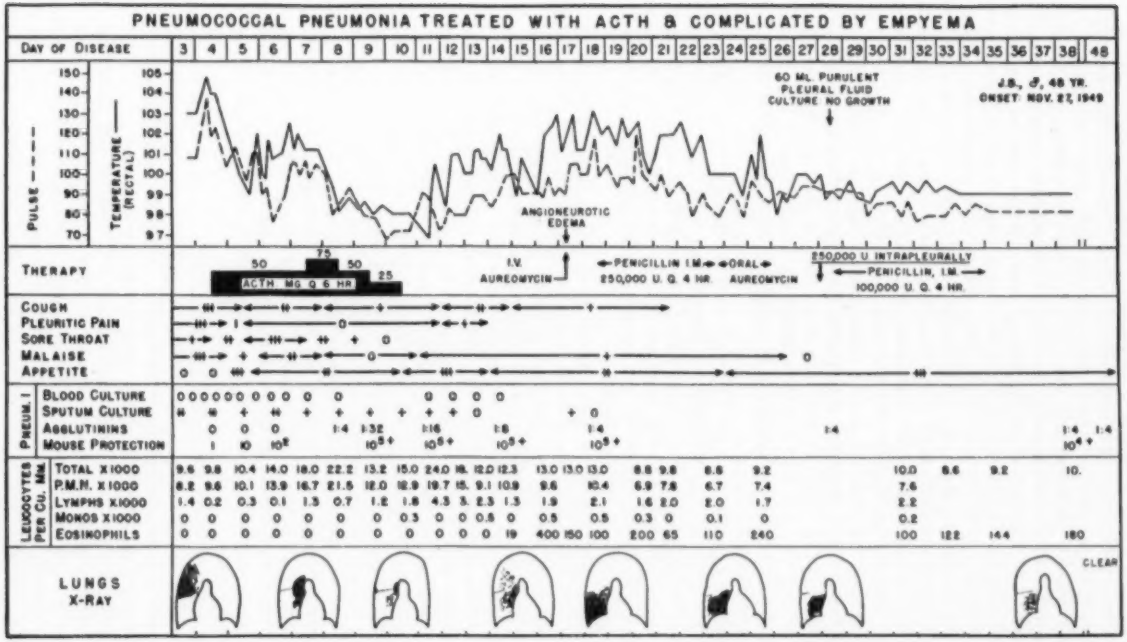

PNEUMOCOCCAL PNEUMONIA TREATED WITH ACTH & COMPLICATED BY EMPYEMA
DAY OF DISEASE
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 48
PULSE
TEMPERATURE (RECTAL)
60 ML. PURULENT PLEURAL FLUID CULTURE NO GROWTH
J.B., ♂, 48 YR. ONSET: NOV. 27, 1949
ANGIONEUROTIC EDEMA
THERAPY
50 75 50 25
ACTH MG. Q 6 HR.
I.V. AUREOMYCIN
PENICILLIN I.M. 250,000 U. Q. 4 HR.
ORAL AUREOMYCIN
250,000 U. INTRAPLEURALLY
PENICILLIN, I.M. 100,000 U. Q. 4 HR.
COUGH
PLEURITIC PAIN
SORE THROAT
MALAISE
APPETITE
PNEUM. I
BLOOD CULTURE
SPUTUM CULTURE
AGGLUTININS
MOUSE PROTECTION
LEUCOCYTES PER CU. MM.
TOTAL X1000
P.M.N. X1000
LYMPHS X1000
MONOS X1000
EOSINOPHILS
LUNGS X-RAY
CLEAR

FIG. 3.

was seen. The signs in the lungs were indeterminate at first, but after the patient had received 1500 ml. of physiologic saline, classical signs of right upper lobe consolidation were readily made out, with increased tactile fremitus, dullness, whispered pectoriloquy, egophony, and crepitant râles over the right upper lobe area. No friction rub was heard. The heart and abdomen were not remarkable save for a slightly tender liver edge, which was palpable 5 cm. below the right costal margin at the midclavicular line. The remainder of the physical examination was not remarkable.

The initial laboratory studies showed the hemoglobin to be 15.0 gm., hematocrit 41 per cent, and white blood count 9600, with 85 per cent polymorphonuclear leukocytes and 15 per cent lymphocytes. The urine was pink in color and showed 1 plus albumin, but no sugar, acetone, or bile. The sediment contained an occasional coarse granular cast and was loaded with leukocytes, but bacteria could not be demonstrated by smear or by culture. The stool was guaiac negative.

The sputum was yellow and grossly mucopurulent, and the smear contained many polymorphonuclear leukocytes and approximately 12 type 1 pneumococci per high dry field. Repeated blood cultures were negative. Blood urea nitrogen was 28, later falling to 18 mg. per 100 ml.; the CO_2 combining power was 54 vol. per cent and chlorides were 79 mEq. Acid-fast bacilli could not be found in the sputum on six different examinations.

The patient was observed for 12 hours with no therapy other than intravenous saline and glucose. During this time his temperature rose to 104.6° F., his pulse to 136, and his respirations to 40. The cough, pleuritic pain, and malaise became more severe, and slight dullness and fine crepitant râles appeared over the right lower lobe. The white blood count was 9800, but there were 98 per cent polymorphonuclear leukocytes. Eosinophiles were absent.

Fifty mg. of ACTH were then administered intramuscularly every six hours. Within 24 hours the patient was afebrile, his pulse rate fell to 92, and the respirations to 24. The cough became less frequent, pleuritic pain subsided, and malaise disappeared, but the pharyngeal injection became more marked and there was some hoarseness. The sputum became rusty and contained about eight pneumococci per field, with no evidence of phagocytosis or of alterations of staining properties of the cocci. The hematologic changes are shown in figure 3 and in table 2. The roentgen-ray and physical findings in the chest were similar to those of the previous day.

During the second day of administration of ACTH, the cough was infrequent and pleuritic pain absent, but the pharyngitis became more severe, with diffuse beefy red injection of the mucous membranes and edema of the uvula and soft palate, but no exudate. Throat cultures yielded type 1 pneumococci and *Streptococcus viridans*. The hoarseness became more marked and the patient complained of sore throat and slight pain on swallowing. Laryngoscopic examination revealed acute, nonexudative laryngitis. The temperature and white count rose slowly and malaise reappeared, but the roentgen-ray and physical findings in the chest showed slight clearing of the right upper lobe.

After receiving 50 mg. of ACTH every six hours for three days, the patient was still febrile but his appetite was good and his complaints were minimal. His sputum was tenacious and purulent and contained an average of 15 pneumococci per high power field. The dose of ACTH was then increased to 75 mg. every six hours for the next 24 hours. The patient promptly became afebrile; the sore throat, pharyngeal injection, and laryngitis began to clear and subsided completely within the next three days. Only occasional pneumococci were found in the sputum after this time, but the white blood cell count rose to 22,000. The consolidation of the lung had resolved considerably. ACTH was, therefore, given in diminishing doses over the next two days, the patient receiving 50 mg. every six hours for 24 hours, followed by 25 mg. every six hours for an additional 24 hours. At the time ACTH was stopped, the

patient was afebrile and asymptomatic. However, his eosinophiles failed to appear as the dose of ACTH was decreased and did not appear until four days after the drug had been stopped. This was in sharp contrast to the experience in the preceding patients.

During the subsequent week the patient again became febrile, his cough became somewhat more severe, and malaise returned. His hematocrit fell to 36, and leukocytosis persisted. He was therefore given 500 mg. of aureomycin hydrochloride in 1500 ml. of saline intravenously. After about 40 mg. of aureomycin had been administered, marked periorbital angioneurotic edema appeared and persisted for 48 hours, with no other symptoms or signs of hypersensitivity. The aureomycin was discontinued and penicillin was given in doses of 250,000 units intramuscularly every four hours for the next six days. During this time there was little change in the temperature, and the signs of consolidation in the right lower lobe increased steadily. The patient was then given aureomycin by mouth, 0.5 gm. every six hours for two days, without untoward effects. However, the irregular fever, slight leukocytosis,

TABLE II

Body Weight and Some Additional Hematological Findings in Case 3

Day of Disease	Hemoglobin grams per ml.	Erythrocytes per cu. mm.	Hematocrit %	Sedimentation Rate (Corrected) mm. per hr.	Weight lb.
3	15.0		41	38	
4	14.5		41	38	
5	15.0		43	38	
6	14.0		38	38	185
7	13.0		37	37	
8	13.0			40	187
9	14.5	4.6*	41		
10	14.5		41	34	181
12	14.5		43	38	179
17	12.5		36		177
24	10.5	3.5	28		174
31	12.0		34		174
38	13.0		37		174

* The mean corpuscular volume was 89 μ^3, mean corpuscular hemoglobin concentration 35%, and the mean corpuscular hemoglobin 31 $\mu\mu$g.; corresponding values on the 24th day were 87, 31 and 27, respectively.

and increasing anemia persisted, and signs of pleural fluid appeared in the right lower chest.

On the twenty-fifth hospital day a thoracentesis yielded 60 ml. of sterile, purulent pleural fluid, and penicillin was then given intrapleurally and intramuscularly. The patient gradually became afebrile, his chest cleared, and he was subsequently discharged.

Inasmuch as the patient had exhibited an immediate anaphylactoid reaction to his initial intravenous dose of aureomycin and no reactions to subsequent oral doses of the antibiotic, it seemed important to determine whether he would again react to parenteral aureomycin. It was considered possible that the initial reaction was the result either of allergens in the injection fluid or of an exaggerated response during a period of hypoadrenalism following cessation of ACTH administration. Before he was discharged from the hospital he was, therefore, given 100 mg. of aureomycin hydrochloride in 150 ml. of 5 per cent dextrose in water, over a period of 50 minutes. Immediately after the aureomycin had run in, the patient sneezed, coughed, and developed facial flush and lacrimation, and infraorbital edema appeared once again. It is of

interest that the eosinophile count performed a few minutes before the first bout of angioneurotic edema was 150 per cu. mm., and about 30 minutes after the edema had appeared an identical eosinophile count was obtained.

Antibodies were demonstrable in significant titers by the mouse protection method on the sixth day of illness, and agglutinins were present on the eighth day. As the empyema developed the agglutinin titer diminished, but the mouse protective titer remained high.

The outstanding features of this case are (1) the initial defervescence and relief from symptoms following the administration of ACTH; (2) the recurrence of fever and symptoms with a second defervescence when the dose of ACTH was increased; (3) the return of fever again when the hormone was finally withdrawn; (4) the persistence of pneumococci in the sputum throughout the period of ACTH therapy and for at least a week thereafter; (5) the persistently elevated sedimentation rate throughout the period of ACTH administration; (6) the development of empyema; (7) the appearance of antibodies at the expected time; (8) the absence of eosinophiles for three days after ACTH was discontinued; (9) the development of angioneurotic edema as a manifestation of hypersensitivity to aureomycin, and (10) the failure to demonstrate a change in the eosinophile count during an episode of acute angioneurotic edema.

Case 4. A 28 year old housewife entered the Boston City Hospital with a history of fever, headache, myalgia, and nonproductive cough of three days' duration. She had received penicillin during these three days, but her symptoms nevertheless increased in severity. At this time the patient's daughter was recovering from an acute respiratory illness of three weeks' duration and the illness was diagnosed as "virus pneumonia."

On entry the patient was prostrated, flushed, and acutely ill. The temperature was 104.2° F., pulse 100, and respirations 24. There was slight dullness over the base of the left lung posteriorly, with bronchovesicular breath sounds in the left axilla and lower half of the left lung field posteriorly. Inconstant post-tussive râles were heard at the left anterior axillary line in the fourth intercostal space. The remainder of the physical examination was negative.

A roentgen-ray film of the chest showed finely nodular diffuse consolidation involving the entire lower lobe of the left lung. The leukocyte count was 3900, with 61 per cent polymorphonuclear leukocytes, 37 per cent lymphocytes, and 2 per cent monocytes. The urine was not remarkable. The sputum was scanty and mucoid, and contained many mononuclear cells, occasional polymorphonuclear leukocytes, and a few gram-positive cocci and gram-negative rods. Sputum and throat cultures taken on three different occasions revealed *Streptococcus viridans, Hemophilus influenzae* and *Neisseria flavus*. Blood cultures were sterile.

The patient was given 100,000 units of penicillin every four hours for the next three days, during which time her temperature rose to 104° F., with downward fluctuations only in response to salicylates or sponge baths.

By the fourth hospital day the consolidation of the left lower lobe had increased and a small area of consolidation had appeared in the right lower lobe near the right cardiac border. The patient was flushed, weak, fatigued, and anorexic. She coughed frequently and complained of generalized myalgia and severe headache. The leukocyte count was 4,900, with 54 per cent polymorphonuclear leukocytes, 42 per cent

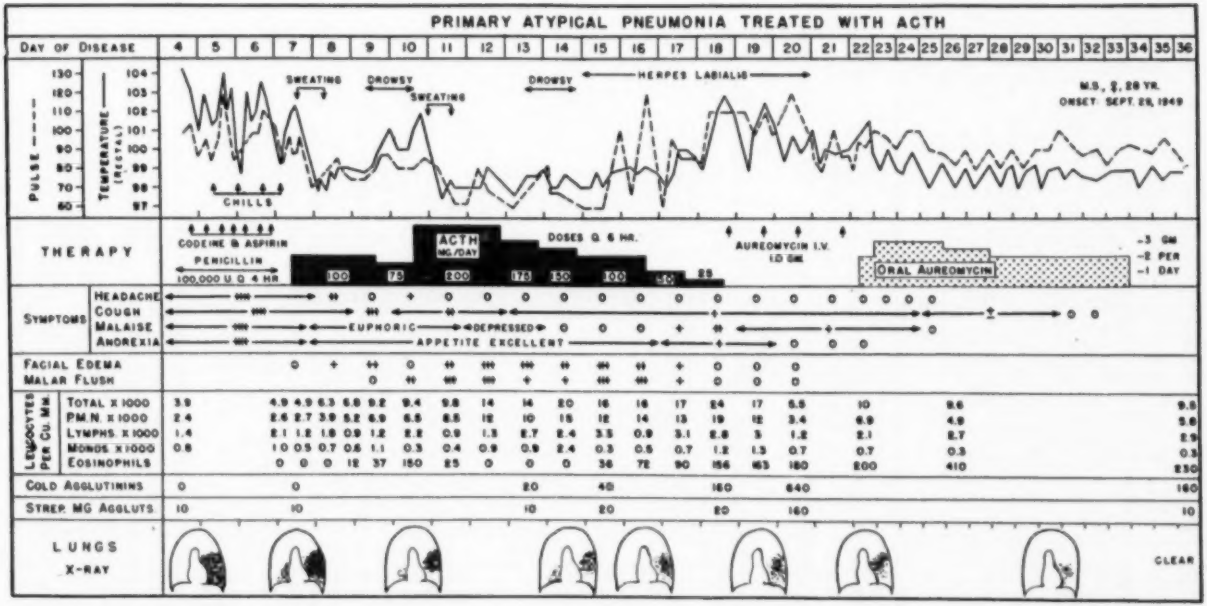

PRIMARY ATYPICAL PNEUMONIA TREATED WITH ACTH
DAY OF DISEASE
PULSE
TEMPERATURE (RECTAL)
SWEATING
DROWSY
SWEATING
DROWSY
HERPES LABIALIS
CHILLS
M.B., ♀, 28 YR.
ONSET: SEPT. 28, 1949
THERAPY
CODEINE & ASPIRIN
PENICILLIN
100,000 U Q 4 HR
ACTH MG/DAY
DOSES Q. 6 HR.
AUREOMYCIN I.V.
1.0 GM
ORAL AUREOMYCIN
-3 GM
-2 PER
-1 DAY
SYMPTOMS
HEADACHE
COUGH
MALAISE
EUPHORIC
DEPRESSED
ANOREXIA
APPETITE EXCELLENT
FACIAL EDEMA
MALAR FLUSH
LEUCOCYTES PER CU. MM.
TOTAL X 1000
P.M.N. X 1000
LYMPHS. X 1000
MONOS. X 1000
EOSINOPHILS
COLD AGGLUTININS
STREP. MG AGGLUTS
LUNGS
X-RAY
CLEAR

FIG. 4.

lymphocytes, and no eosinophiles. The hematocrit was 40 and the hemoglobin 12.4 gm.

The patient was given 25 mg. ACTH every six hours, and within 12 hours the temperature began to fall and diaphoresis appeared. Within 18 hours the patient was afebrile and exhibited a definite sense of well-being, freedom from myalgia and headache and a good appetite, but she was still coughing frequently. The signs in the lungs were unchanged. The hematologic studies (figure 4 and table 3) showed some leukocytosis, lymphopenia, and absence of eosinophiles. On the second day of therapy, malar flush and slight facial edema appeared and 12 eosinophiles per cu. mm. were found. The daily dose of ACTH was decreased to 75 mg. in four divided doses, and the temperature promptly rose to 101.8° F., mild headache reappeared, and there was marked diuresis, with a loss of 5.5 lb. in weight overnight. The hematocrit increased from 35 per cent to 39 per cent; the leukocyte count rose to 10,000 with 75 per cent polymorphonuclear leukocytes and 15 per cent lymphocytes, and 150 eosinophiles per cu. mm. appeared.

The dose of ACTH was therefore increased to 50 mg. every six hours, and within 12 hours the patient was once again afebrile, euphoric, and free of symptoms. She again became oliguric and regained six pounds. Her cough persisted but was less

TABLE III

Body Weight and Some Additional Hematologic Findings in Case 4

Day of Disease	Hemoglobin grams per ml.	Hematocrit %	Sedimentation Rate (Corrected) mm. per hr.	Weight lb.
7	12.4	40	33	
8	11.5	38.5	31	
9	10.4	35	31	144
10		39	30	138
12	10.1	34	31	145
15	11.6	36	28	146
19	12.4	42.5	30	138
22	11.8	40	34	
36	12.0	40.5	33	139

severe, and physical signs and roentgen-rays of her chest were consistent with slight clearing in the left lower lobe. Eosinophiles were absent. The dose of ACTH was continued at 200 mg. per day for two days, whereupon marked facial edema and malar flush reappeared and the patient became quite depressed. The dose was, therefore, gradually decreased over a period of six days and then stopped. During the period of withdrawal of ACTH, as during the earlier period when the dose had been decreased, the patient was drowsy but otherwise felt well.

The roentgenograms of the chest showed slow but steady clearing, and the cough persisted, with steadily diminishing severity. The leukocyte count rose during the second and third weeks of illness to a peak of 24,000 per cu. mm. and slowly returned to normal levels.

Following the last dose of ACTH the temperature rose to 102.8° F. and the patient felt weak, listless, and depressed. Her cough had not become worse and the chest was clearing steadily. Repeated sputum examinations revealed only *S. viridans* and rare polymorphonuclear leukocytes.

The patient was given 1 gm. of aureomycin intravenously daily for four days, followed by 2 to 3 gm. of aureomycin daily for 12 days. The leukocyte count decreased and the eosinophile count remained within normal limits, but the fever responded very slowly and irregularly and the patient was not afebrile until one week after the onset of therapy with the antibiotic. The subsequent course was uneventful.

Cold agglutinins and Streptococcus MG agglutinins first developed during the third week of the illness and increased later to a maximum titer of 1:640 and 1:160, respectively.

A few additional aspects of the course in this patient deserve mention. Herpes labialis appeared during the time that ACTH was being withdrawn and persisted for one week. Also, while the patient was receiving 50 mg. ACTH every six hours, she developed hyperglycemia and glycosuria; these cleared as the dose of ACTH was decreased. The blood pressure, which was determined twice daily, showed no significant changes. The patient's menstrual period, which was due during the course of the illness, did not occur, but on the following month a normal menstrual flow occurred at the expected time and no menstrual disturbances were observed during the subsequent three months.

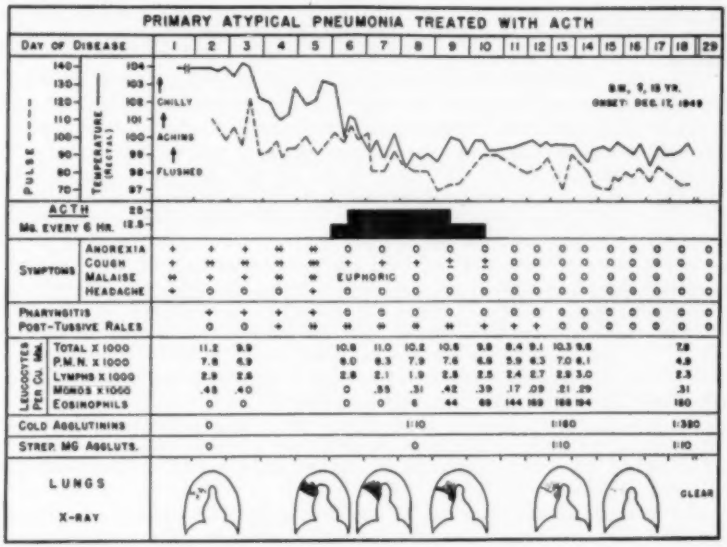


FIG. 5.

The significant features of this case are (1) the prompt defervescence and remission of all symptoms except cough; (2) the "escape" from ACTH with diuresis, exacerbation of symptoms, and return of fever and eosinophiles in the blood; (3) the absence of fever and symptoms after the dose of ACTH was increased, with exacerbation again when the hormone was finally withdrawn; (4) the slow resolution of the pneumonitis, which was initially of unusual severity; (5) the appearance of cold agglutinins and Streptococcus MG agglutinins at the usual time; (6) the appearance of herpes labialis while ACTH was being administered; (7) the lack of effect of ACTH on the erythrocyte sedimentation rate; (8) the failure of the patient to respond to aureomycin administered after ACTH was withdrawn, and (9) the appearance of hyperglycemia and glycosuria during the period of treatment.

Case 5. A 15 year old schoolgirl entered the Boston City Hospital one day after the sudden onset of chilly sensations, nonproductive cough, headache, and generalized myalgia. The past, family and social histories were noncontributory. At entry her temperature was 104° F., pulse 110, respirations 22, and blood pressure 110/68 mm. Hg. Her skin was flushed and there were multiple acneform lesions on her face and shoulders. Physical examination revealed no other noteworthy findings. The chest was clear to inspection, palpation, percussion, and auscultation. A roentgenogram of the chest showed mild infiltration of the right upper lobe.

Laboratory studies revealed a normal urine, 12.5 gm. hemoglobin, and 11,200 leukocytes per cu. mm., with 70 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes, and 4 per cent monocytes. The blood urea nitrogen was 13 mg. per cent, the Hinton and heterophile tests were negative, and the initial cold agglutinin and Streptococcus MG agglutinin tests were negative. Several throat cultures yielded only *Streptococcus viridans* and *N. catarrhalis*, and four blood cultures showed no growth. Tuberculin patch tests and old tuberculin (1–1000) intradermally gave no reactions.

The patient was observed for three days, during which time her symptoms became more severe, her cough increased in frequency, and anorexia became more marked. The temperature, which had fallen from 104° to 101° F., rose again to 103°, and slight dullness and showers of post-tussive râles appeared over the right scapular spine. Roentgen examination on the third hospital day revealed that the area of infiltration in the right upper lobe had become larger and much denser since entry. The white blood count was 10,800 per cu. mm., with 74 per cent polymorphonuclear leukocytes, and there were still no eosinophiles.

ACTH was administered at six hour intervals, beginning with two doses of 12.5 mg. each, followed by 25 mg. per dose for 72 hours, and 12.5 mg. per dose for an additional 24 hours. Within 24 hours, the patient was afebrile and free of all symptoms save for slight residual cough. The infiltrative process cleared slowly but steadily, both by physical signs and by roentgen-ray, and at the time of discharge the patient's chest was essentially clear. The acne did not change significantly in severity or distribution during or after treatment with ACTH.

The patient underwent remarkable psychologic changes: she was shy and withdrawn prior to institution of treatment, became quite outgoing and emotionally demonstrative during the course of treatment, and regressed to her original status after ACTH was withdrawn.

The hematologic findings changed very little and the leukocyte count, which was only slightly elevated, returned to normal after several days. Eosinophiles made their appearance during the last three days of treatment and then increased to normal levels after the treatment with ACTH was stopped. Cold agglutinins in a titer of 1:160 were demonstrated on the thirteenth day of illness, and the titer of Streptococcus MG agglutinins on that day was only 1:10 and did not increase in later specimens of blood.

The outstanding features of this case: (1) defervescence and remission of symptoms were prompt after ACTH was administered; (2) resolution of the pneumonitis was not significantly affected by treatment; (3) acne was not increased by ACTH, and (4) cold agglutinins and Streptococcus MG agglutinins appeared at the usual time.

Discussion

The administration of adrenocorticotropic hormone to three patients with pneumococcal pneumonia and two with "viral" pneumonia was followed

by prompt remission of the clinical symptoms associated with the acute illness, but the remissions were not lasting in every case. In each patient, administration of the hormone was followed within 12 to 24 hours by diaphoresis, defervescence, and marked subjective improvement. These were preceded in some cases by a brief exacerbation of symptoms, during which the temperature, pulse, and respirations increased and general toxicity was intensified.

In the cases of pneumococcal pneumonia, pneumococci were abundantly present in the sputum after the patients had become afebrile and asymptomatic, and in one patient bacteremia was demonstrated on two successive occasions 12 and 36 hours after the patient had become clinically well. Rusty sputum was first noted in that patient after he had become afebrile, and similar sputum was raised for as long as five days after the apparent remission of the acute illness in the second case of pneumococcal pneumonia.

The number of cases studied is manifestly too small to permit valid comparisons with data obtained in previous studies of large numbers of similar cases of "untreated" pneumonias. However, it seems quite unlikely that the defervescence observed in these cases would have occurred spontaneously coincident with the administration of ACTH. In 105 cases of untreated type 8 pneumococcal pneumonia observed at the Boston City Hospital, there were no instances of defervescence during the first two days and only two cases in which recovery by crisis occurred during the third day of illness.[4] Among 69 untreated type 2 pneumococcal pneumonias studied at this hospital, there was only one in which the patient became afebrile in less than four days.[2] Further evidence favoring a causal relationship of ACTH to the defervescence derives from the course of events in patients 3 and 4; in these patients, fever diminished following the onset of therapy, then increased while therapy was being continued, but again declined sharply as the dose of ACTH was increased, and finally rose when ACTH was withdrawn.

The latter observations suggest that ACTH may have an antipyretic action. Such an antipyretic effect was indeed demonstrated, both in man and in rabbits, by using bacterial and viral pyrogens.[6] Only in patient 5, in whom the treatment of primary atypical pneumonia with ACTH was begun on the fifth day, does it appear at all likely that the remission of fever might have occurred spontaneously at the time that ACTH was administered.

There is no evidence that ACTH or the cortical hormones exert a direct effect on the infectious agents. Quantitative counts of the numbers of pneumococci in the sputum taken before and after defervescence usually showed an initial increase, followed by gradual diminution in the numbers of microörganisms. Furthermore, as long as they were demonstrable, the pneumococci were not phagocytosed by the many polymorphonuclear leukocytes which were present in the sputum, and there was no alteration in the staining characteristics of the pneumococci such as usually occurs following treatment of pneumococcal pneumonias with antibacterial agents.

Observations on the etiologic agent were not possible, of course, in the cases of primary atypical pneumonia. It is of interest, however, that patient 4 developed herpes simplex while she was receiving ACTH. Preliminary studies in this laboratory with influenza viral infection in mice also indicate that ACTH does not affect viral multiplication adversely. It can be concluded that the observed sequelae to the administration of ACTH were due to an effect exerted on the host and not on the etiologic agents.

To what degree ACTH acts either by stimulating the defensive mechanisms in the host, or merely by setting in motion mechanisms which have only relatively secondary effects that result in obscuring the clinical signs and symptoms, is difficult to determine at present. In patients 1 and 2, an induced "crisis" seemed to have occurred and the clinical course thereafter was not remarkable in each instance, despite the presence of bacteremia after the "crisis" in one and the persistence of rusty sputum in the other. The rapid disappearance of myalgia, pleuritic pain, headache, drowsiness, malaise, and other evidence of toxemia as a consequence of adrenocortical stimulation would suggest that the hormones affected the responses of the host to the infection in a beneficial manner. On the other hand, patient 3 developed empyema and patient 4 had a protracted febrile course after ACTH was withdrawn. Patient 3, however, was an alcoholic with type 1 pneumococcal pneumonia, and thus was particularly prone to develop complications of his infection.[1]

Patient 3 also developed angioneurotic edema immediately after the administration of a small dose of aureomycin intravenously. This unusual toxic effect occurred one week after ACTH was withdrawn; it recurred and was accompanied by sneezing and generalized itching when the patient was given a test dose of aureomycin intravenously several weeks later.

It was of interest to determine the time of appearance of antibodies in these patients in relation to the administration of ACTH. Although the data are to be interpreted with caution in such a small group, antibodies appeared in each of the cases of pneumococcal pneumonia at a time which might ordinarily have been expected in patients who recover spontaneously from similar infections. Cold agglutinins also appeared at the expected time in the cases of viral pneumonia.

Clearing of the chest occurred with unusual rapidity in Case 1, and was unduly delayed in the case with empyema. In the other three patients, however, the clearing of the pulmonary lesion seemed to be neither accelerated nor delayed.

Circulating eosinophiles could not be demonstrated in any of the patients during the initial acute stage of the illness, but were readily demonstrated after ACTH was withdrawn, with one exception. In patient 3, who developed empyema, eosinopenia persisted for several days after the hormone was discontinued.

Some of the doses of ACTH that were used were quite large. It was reasoned that the acute illness exerted a stress of such magnitude that large

amounts of cortical stimulation would be required to exceed that which was induced by the infection itself. This assumption is supported by the course of events in patients 3 and 4, who did not remain afebrile while they were receiving the initial doses of ACTH and required increasing doses of the hormone to reduce their fever. The subsequent course in both of these patients was complicated by persistence of some infection. Patient 4 "escaped" from the effects of ACTH while she was receiving the hormone, as manifested by the appearance of eosinophiles, reappearance of fever, diuresis, and loss of weight. Further studies will be necessary to reveal whether the initial failure to induce a "crisis" with ACTH may be interpreted as an indication of a deficiency in the resistance of the host to the infection and hence a harbinger of future complications. In any event, the patient with empyema and patient 4 with viral pneumonia demonstrate that ACTH is not to be considered an effective form of therapy for bacterial or viral pneumonias comparable to specific antibiotics or chemotherapy.

This presentation has been limited to the clinical, bacteriologic and immunologic aspects of the cases studied. Of the known effects of the cortical hormones, however, those affecting metabolic processes appear to be most prominent. Studies of electrolyte and nitrogen metabolism have been carried out in these and in other patients. Although most of the effects noted by other workers, and possibly some additional ones, have been demonstrated in these patients, they have failed thus far to elucidate the fundamental mechanisms involved in the recovery from these infections. Further studies of these aspects are continuing.

Summary and Conclusions

Three patients with pneumonia due to types 8, 2, and 1 pneumococci, respectively, and two with primary atypical pneumonia were treated with pituitary adrenocorticotropic hormone. Defervescence and relief from symptoms and signs of toxemia occurred promptly in all cases. In three instances the patients remained asymptomatic and afebrile, despite the persistence of bacteremia in one and the continued production of rusty sputum in another.

One patient with pneumococcal pneumonia experienced an exacerbation of symptoms while receiving ACTH, with remission when the dose was increased. This patient had an extension of his pulmonary lesion and later developed empyema. One patient with viral pneumonia had a similar exacerbation of symptoms while receiving the hormone, with prompt relief from all symptoms except cough when the dose of ACTH was increased, but with return of fever and malaise after ACTH was withdrawn.

No evidence was obtained of any bactericidal action exerted by adrenal steroids.

Antipneumococcal antibodies and cold agglutinins appeared at the anticipated time, with no evidence of acceleration or delay in their production.

Eosinophiles were uniformly absent in all cases during the acute stages of the illness and returned either after the dose of ACTH was reduced or, as in one case, when the patient developed tolerance to the administered dose of the hormone and "escaped" from its effects. Clearing of the pulmonary lesions may have been accelerated in one patient and delayed in another, but in the remaining three patients resolution of the pneumonic process seemed to have been neither accelerated nor delayed.

All the patients manifested euphoria and a sense of well-being at some time while they were receiving the drug. Two developed glycosuria, two developed facial edema, and all demonstrated some degree of bradycardia, but none showed any significant alterations of blood pressure or sedimentation rate attributable to the ACTH.

It is concluded that ACTH may, in some instances, induce profound changes in the clinical symptoms of patients with acute infections without demonstrably affecting the etiologic agent. There was no evidence from these cases of any effect on the production of specific antibodies.

The significance of these findings is not clear. They suggest that the greater production of adrenal steroids may augment those metabolic processes which are active in the cellular responses to infection.

ACKNOWLEDGMENTS

The authors are indebted to Clare Wilcox and Mildred W. Barnes for technical assistance.

BIBLIOGRAPHY

1. Cecil, R. L., Baldwin, H. S., and Larsen, N. P.: Lobar pneumonia. A clinical and bacteriologic study of 2000 typed cases, Arch. Int. Med. **40**: 253–280, 1927.
2. Finland, M., and Dowling, H. F.: Pneumococcus type II and type V infections, Arch. Int. Med. **58**: 598–619, 1936.
3. Finland, M., Kass, E. H., and Ingbar, S. H.: Effects of ACTH in primary atypical (viral) pneumonia and in pneumococcal pneumonia (Preliminary report). In Proc. 1st Clinical ACTH Conference, Ed. J. R. Mote, Philadelphia, Blakiston Co., 1950, pp. 529–535.
4. Finland, M., and Sutliff, W. D.: Infections with pneumococcus type III and type VIII, Arch. Int. Med. **53**: 481–507, 1934.
5. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions, Arch. Int. Med. **85**: 545–666, 1950.
6. Kass, E. H., and Finland, M.: Effect of ACTH on induced fever, New England J. Med., in press.
7. Kass, E. H., Ingbar, S. H., and Finland, M.: Renal glycosuria induced by adrenocorticotropic hormone, Proc. Soc. Exper. Biol. and Med. **73**: 669–672, 1950.
8. Randolph, T. G.: Blood studies in allergy. I. The direct counting chamber determinations of eosinophils in propylene glycol-aqueous stains, J. Allergy **15**: 89–93, 1944.
9. Thorn, G. W. et al.: The clinical usefulness of ACTH and cortisone, New England J. Med. **242**: 783–793, 824–834, 865–875, 1950.
10. White, A.: Relation of adrenals to immunity, Bull. New York Acad. Med. **24**: 26–31, 1948.

A CLINICAL APPRAISAL OF NEOMYCIN *

By Burton A. Waisbren, M.D., and Wesley W. Spink, M.D., F.A.C.P.,
Minneapolis, Minnesota

Neomycin, an antibiotic derived from a strain of streptomycetes that is closely related to *Streptomycetes fradiae,* was discovered by Waksman and Lechevalier in 1949.[1] It was a product of their search for an antibiotic that would be effective against streptomycin-resistant bacteria, particularly tubercle bacilli. Little has been reported as to the chemical nature of neomycin other than that it is a basic compound, heat stable, and is resistant to the action of acid (pH 2) at the temperature of boiling water.[1]

Studies on the spectra of bacteria affected by neomycin have revealed the drug to be bactericidal in vitro against a wide variety of both gram negative and gram positive organisms.[1, 2, 3, 4, 5] Investigations in which neomycin has been compared with other antibiotics have indicated that it might be the antibiotic most effective against infections due to *Proteus vulgaris.*[2, 4, 10] In addition to being active against streptomycin-resistant organisms, neomycin differs from streptomycin in that, in a large population of bacteria, the rapid appearance of resistant strains that occurs with the use of streptomycin may not occur following the administration of neomycin.

Although in the original report [1] neomycin was found to "have limited toxicity to animals or none," more recent studies have indicated that the drug has a nephrotoxic effect on guinea pigs and mice.[6, 7]

Neomycin has been under clinical investigation at the University of Minnesota Hospitals during the past year, and the following is a report of a trial of neomycin in 63 patients having different types of infection, including those due to *Mycobacterium tuberculosis* and *Proteus vulgaris.* In addition to the therapeutic results, there is presented a study of the concentration and distribution of neomycin in the body fluids; the in vitro sensitivities of several of the invading microörganisms, and evidences of toxicity.

Materials and Methods

The criteria for initiating therapy with neomycin was a culturally proved infection that would be expected to respond to the drug and, in most cases, infections that had not responded to therapy with other antibiotics. The ages of the patients ranged from nine months to 93 years of age, with 22 of them being over 60 years of age. Thirty-four patients were males and 29 females. Albuminuria was present before therapy in 36 of the patients. The types of infections treated are noted in table 1.

* Received for publication June 30, 1950.
From the Department of Medicine of the University of Minnesota Hospitals and Medical School, Minneapolis.

The neomycin * employed consisted essentially of a single component as determined by paper chromatography. In most instances, patients were given intramuscular injections four times a day of 0.5 gm. of neomycin dissolved in 2 ml. of sterile physiologic saline solution.

All material for culture was sent to the bacteriologic laboratory of the University Hospitals, where the organisms were isolated and identified.

The sensitivities of the bacteria to various antibiotics were determined by a tube-dilution method. One-half ml. aliquots of a 1–100 dilution of an 18 hour growth in tryptose soy broth were added to tubes containing 0.5 ml. of decreasing concentrations of drug. The end point was determined by selecting that tube with the lowest concentration of antibiotic in which visual growth of the organism was inhibited for 18 hours.

TABLE I

Types of Infections Treated with Neomycin

Diagnosis	Number of Cases Treated
1. Tuberculosis	7
2. Urinary Tract Infections	
Proteus vulgaris	17
Pseudomonas aeruginosa	11
Aerobacter aerogenes	8
Escherichia coli	5
3. Bacteremia Due to Gram Negative Bacilli	3
4. Staphylococcic Infections	2
5. *Proteus morganii* in the Stool	1
6. Chronic Pulmonary Disease	7
7. Peritonitis Due to *Proteus vulgaris*	2
8. Infections of Unknown Etiology	3
Total	66*

* The total number is 66 when only 63 patients were treated, because one patient was given two courses of neomycin for different diseases and two of the urinary tract infections were caused by more than one species of bacteria.

The concentrations of neomycin in the serum of patients were also determined by a tube-dilution method. A strain of *Bacillus subtilis* was used as the test organism. Two rows of tubes (13 mm. by 100 mm.) were employed; one contained two-fold dilutions in tryptose phosphate broth of a known amount of neomycin dissolved in serum obtained from the patient before therapy; the other row of tubes had two-fold dilutions of the serum in which the neomycin concentration was to be determined. To both sets of tubes were added 0.5 ml. of a 1:1000 dilution of an 18 hour growth of the test organism in tryptose phosphate broth. The concentration of neomycin in the serum was calculated by multiplying the concentration of neomycin that would inhibit the test organism by the dilution of the serum that gave the same inhibition. It was found that neomycin dissolved in broth gave the same end point as neomycin dissolved in serum, so broth controls were used in later determinations. Determinations of neomycin concentration in the cerebrospinal fluid and pleural fluid were made in a similar man-

* Prepared and supplied by the Upjohn Company.

ner, using control fluids from the same patient whenever possible. The finding that a number of urines, when highly diluted, inhibited the test organism without the addition of neomycin made the determinations of neomycin concentration in the urine by this method too inaccurate for use.

Clinical Results

1. *Tuberculosis.* Investigations with mice infected experimentally with tubercle bacilli had indicated that neomycin probably was not as effective as streptomycin and dihydrostreptomycin,[8] but that it "warranted further study from the experimental and clinical viewpoint." [9]

Two criteria suggested by Hobson and McDermott [10] as useful in evaluating drugs for tuberculosis were used in this study. The first was the treatment of miliary and meningeal tuberculosis in which an end point of death was certain without therapy, and the second was an attempt to determine whether organisms isolated during and after therapy had become resistant to the drug being used.*

Seven patients with tuberculosis were treated with neomycin (table 2). Three patients had miliary tuberculosis; two had tuberculous meningitis; one had acute tuberculous empyema, and one had a chronic draining tuberculous sinus.

Case Reports

Case 42. The patient was a two year old female who entered the University Hospitals because of fever of 10 days' duration. A diagnosis of miliary tuberculosis and tuberculous meningitis was established by a positive Mantoux test, characteristic spinal fluid findings, and the presence roentgenographically of a fine mottling throughout the right lung. Neomycin therapy was instituted on the third hospital day, with a dose of 250 mg. being given intramuscularly every eight hours. When no response was noted, the dose of neomycin was raised to 500 mg. three times per day. The child continued to exhibit a high spiking fever, so additional therapy with promizole and streptomycin was begun. While there was a questionable response to this, it was short lived and the child's temperature became higher each day, with death occurring on the twenty-first hospital day. Anuria occurred the day prior to death. During the last nine days of life the daily administration of 1.5 gm. of neomycin, 750 mg. of streptomycin, and 1.5 gm. of promizole had no effect on the severity of the course of the infection. The concentration of neomycin in the spinal fluid prior to the administration of the other drugs was 1.25 mcgm./ml. The serum concentration of neomycin at the same time was 4.9 mcgm./ml.

Postmortem findings revealed miliary tubercles throughout the lungs, spleen, liver, and kidneys; hepatomegaly, and a pericardial effusion. Sections of the kidneys revealed marked destructive lesions of the tubules.

Case 63. The patient was a nine months old male who entered the University Hospitals because of cough, fever, anorexia, and stiff neck of three weeks' duration. Characteristic cerebrospinal fluid findings, a positive Mantoux test, and scattered pulmonary lesions established the diagnosis of miliary tuberculosis and tuberculous meningitis. Therapy with dihydrostreptomycin and promizole was started on the

* Determinations of the drug sensitivities of the tubercle bacilli were done by Dr. Wendell Hall, who used a tube dilution method in Dubois' tween 80 media.

TABLE II

Summary of Seven Cases of Tuberculosis Treated with Neomycin

No. Age Sex	Duration Diagnosis Outcome	Daily Dose Neomycin	Days of Therapy	Other Treatment			Cerebrospinal Fluid Findings			Neomycin Levels mcgm./ml.		Postmortem
				Drug	Dose	Days	Lab Procedure	Before Neomycin	After Neomycin	Blood	CSF	
42 2 yr. F	31 days Miliary Tb. Death	0.75 gm. 1.5 gm.	15–16th day 16–31st day	Sulfa Aureo Promi- zole	2 gm. 200 mg. 1.5 gm.	12–15 12–14 17–31	WBC PMN mono Protein Sugar	180 37% 63% 70 mg. % 39 mg. %	34 46% 46% 39 mg. % 32 mg. %	4.9	1.25	Miliary tb. lungs, liver, spleen. Tubular damage in kidneys
63 9 mo. M	210 days Miliary Tb. Death	200 mg. 10 mg. (intra-thecally)	63–152nd day 146–152nd day	Dihydro Promi- zole	320 mg. 500 mg.	2–57th 2–99th	WBC PMN mono Protein Sugar	23 87% 13% 231 mg. % 8	350 82% 18% 199 mg. % 6	4.9	2.5	Healing miliary lesions in lung. Fibrinous exudate over base of brain. Organism cultured inhibited by 10 mcgm./ml. of neomycin
15 60 yr. M	5 days Miliary Tb. Death	2 gm. I.M. 25 mg. (intra-thecally)	3–5th day 5th day	None			WBC PMN mono Protein Sugar	3810 87% 13% 353 mg. % 14	189 61% 33% 218 mg. % 9			Tuberculoma in frontal lobe. Tubercles in nodes, lungs, kidneys, spleen

TABLE II—*Continued*

No. Age Sex	Duration Diagnosis Outcome	Daily Dose Neomycin	Days of Therapy	Other Treatment			Cerebrospinal Fluid Findings			Neomycin Levels mcgm./ml.		Postmortem or Follow-Up
				Drug	Dose	Days	Lab Procedure	Before Neomycin	After Neomycin	Blood	CSF	
37 11 yr. F	14 days Tb. meningitis Death	1 gm. I.M. 2 gm. I.M.	4–7th day 7–14th day	Dihydro Promizole	1 gm. 2 gm.	12–14 12–14	WBC PMN mono Protein Sugar	249 20% 80% 189 mg. % 10	86 32% 54% 113 mg. % 32	2.5	1.25	Tuberculous encephalitis and meningitis. Gelatinous membrane at base of brain. Organism isolated before and after Rx inhibited by 3.5 mcgm. of neomycin
50 17 yr. F.	90 days Tb. meningitis Death	2 gm. I.M.	87–90th day	Aureo Strepto	1 gm. I.V. 2 gm. I.M.	86–88th 86–88th	WBC PMN mono Protein Sugar	56 14% 86% 390 mg. % 41 mg. %	167 2% 98% 320 mg. % 53 mg. %			No post-mortem. Tb. bacilli cultured from spinal fluid
60 42 yr. M	21 days Tb. empyema. Hospitalized elsewhere	2 gm. I.M.	18–21st day	None						20	Empyema fluid 10	Tubercle bacilli cultured from chest fluid containing 10 mcgm./ml. of neomycin
35 61 yr. F	365 days Scrofula followed dispensary	2 gm. I.M.	350–365th day	Strepto	1 gm.	220–280th day						Moderate improvement. Acid fast bacilli on smear during therapy

Sulfa—Sulfadiazine.
Aureo—Aureomycin.
Strepto—Streptomycin.
Dihydro—Dihydrostreptomycin.

second hospital day. The dose was 320 mg. of promizole each day. In addition, 10 mg. of dihydrostreptomycin was injected intrathecally every other day until 21 injections had been given. Although the child became essentially afebrile, the lack of gain in weight, the persistence of spinal fluid abnormalities, and general lethargy indicated that the infection was not under control. Therefore, after promizole and streptomycin had been administered for 55 days, the child was started on a daily dose of 200 mg. of neomycin. This was continued for 89 days. The neomycin concentration in the spinal fluid was 2.5 mcgm./ml. In spite of this therapy, the patient gradually became worse, his mental faculties were obviously retarded, and he died on the one hundred eighty-second hospital day. Postmortem examination revealed a thick yellow gelatinous membrane covering the entire base of the brain. Tubercle bacilli cultured from this exudate were inhibited by 10 mcgm./ml. of streptomycin and 10 mcgm./ml. of neomycin. Microscopic examination of the kidneys revealed normal architecture and no evidence of tubular damage.

Case 15. The patient was a 60 year old white male who was admitted to the University Hospitals because of a draining sinus in his neck. In addition, he had had disabling rheumatoid arthritis for many years. The patient's first month in the hospital was relatively uneventful, and he received roentgen-ray therapy to the sinus. Five days before death he suddenly became febrile and lapsed into a coma. A lumbar puncture performed the day prior to death revealed acid-fast bacilli in the cerebrospinal fluid, and a protein concentration of 353 mg. per 100 ml. Therapy with neomycin was started at this time but his fever rose to 106° F., and he died after receiving 2.5 gm. of neomycin intramuscularly and 25 mg. intrathecally. Tubercle bacilli were cultured from the spinal fluid obtained just before death although the patient had received two grams of neomycin in the preceding 24 hours. Postmortem study demonstrated a tuberculoma in the right frontal pole of the cerebral hemisphere, tuberculous meningitis, pulmonary tuberculosis, scrofula, and minimal tuberculosis of the kidney and spleen. No microscopic evidence of kidney tubular lesions was detected.

Case 37. The patient was an 11 year old child who entered the University Hospitals because of headache, stiff neck, and fever of three days' duration. Three years previously the child had been given streptomycin for three months because of tuberculous meningitis. Following this she had been well until the time of the present illness. Her mother had just entered a sanatorium because of active pulmonary tuberculosis. The clinical impression of tuberculous meningitis was substantiated by isolating tubercle bacilli from the cerebrospinal fluid, and neomycin therapy was started within 24 hours of admission. The initial dose was one gram per day, but this was raised to two grams per day when after 72 hours no response was apparent. Two grams per day of neomycin were given until the seventh hospital day when, because the patient continued to have a spiking fever and became increasingly lethargic, therapy with promizole and streptomycin was begun. During the last three days of life, chemotherapy consisted of daily injections of two grams of neomycin, one gram of streptomycin, and two grams of promizole. Death occurred on the eleventh hospital day. Prior to the addition of the other drugs, the neomycin concentrations in the serum and spinal fluid were 2.5 mcgm./ml. and 1.25 mcgm./ml., respectively. Tubercle bacilli recovered before treatment and after death were inhibited by 3.5 mcgm. of neomycin. Postmortem examination revealed a diffuse tuberculous meningitis and encephalitis. There was no microscopic evidence of tubular damage in the kidneys.

Case 50. The patient was a 17 year old girl who was transferred to the University Hospitals with a presumptive diagnosis of brain tumor. She had been complaining of headaches for the three months prior to admission and had had an intermittent fever. Previous therapy had included aureomycin, penicillin, and strepto-

mycin. The latter drug was stated to have caused some improvement. On admission a diagnosis of encephalitis was entertained, but during the first 15 days in the hospital she became steadily worse. She was then treated for tuberculous meningitis. She was given streptomycin from the seventeenth to the nineteenth hospital days, and neomycin from the eighteenth day to death on the twenty-first hospital day. A specimen of her spinal fluid injected into a guinea pig on the seventeenth hospital day yielded tubercle bacilli. No tubercle bacilli were recovered from the fluid on the nineteenth day. This was the only indication of any possible beneficial effect of therapy. Permission for post mortem was not granted.

Case 60. The patient was a 42 year old male who entered the University Hospitals Out-Patient Department with acute tuberculous empyema. He was given neomycin for three days while arrangements for sanatorium care were being made. The dose was 2 grams per day, which resulted in a serum concentration of 20 mcgm./ml. and a pleural fluid concentration of 10 mcgm./ml. In spite of this concentration of neomycin, the patient continued to be febrile and acutely ill. In addition, tubercle bacilli were cultured from the specimen of pleural fluid that contained a concentration of 10 mcgm./ml. of neomycin.

Case 35. The patient was a 61 year old white woman who entered the University Hospitals for treatment of scrofula of one year's duration. She had received streptomycin therapy for two months prior to admission, but this had been stopped because of the onset of dizziness. The patient was given 2 grams per day of neomycin for 15 days without improvement in her lesions. Acid-fast bacilli were seen on a smear of the exudate before and during therapy. No symptoms or signs of toxicity evidenced themselves during this course of therapy.

Summary. In none of the seven cases of tuberculosis was there any evidence of beneficial response to therapy with neomycin. Tubercle bacilli were cultured from four cases during or after treatment. In three of these four cases, significant concentrations of neomycin were demonstrated in the body fluids. These findings suggested that neomycin alone is of doubtful value in the treatment of acute tuberculosis.

2. *Urinary Tract Infections.* The effectiveness of aureomycin and chloramphenicol against infections of the urinary tract caused by *Escherichia coli* and *Aerobacter aerogenes* has increased the frequency with which *B. proteus* and *Pseudomonas aeruginosa* are cultured from the urinary tract. It has not been an uncommon experience to treat a patient successfully with aureomycin for an infection caused by *E. coli* or *A. aerogenes*, only to have *B. proteus* or *P. aeruginosa* appear in subsequent urine cultures. As will be pointed out shortly, the successful eradication of proteus from the urinary tract is not infrequently followed by the appearance of *P. aeruginosa*. It is not known whether this is due to the fact that the infections initially are caused by more than one species of bacteria, and culture methods favor the isolation of certain bacilli, or whether it is due to rapid reinfection. A study is now in progress in this laboratory in which an attempt is being made to follow patients with chronic urinary tract infections for an extended period. Preliminary results show a high rate of recurrence and also that the sterilization of the urine by treatment with antibiotics is in most cases transient. The following observations are advanced as evidence that neomycin has a definitely beneficial effect on the organism involved in these chronic cases,

TABLE III

Treatment of Urinary Tract Infections Due to Proteus Organisms with Neomycin

No. Age Sex	Diagnosis	Previous Therapy	Daily Dose Neomycin in Grams, Duration of Therapy	No. of Cultures Before Treatment	Cultures During and After Treatment	Sensitivities of Organisms in mcgm./ml.				Neomycin Concentration in Serum, mcgm./ml.
						Neo.	Chloro.	Aureo.	Q-19	
3 32 M	Chr. pyelonephritis. One kidney	Aureomycin Sulfonamide	2 gm. 6 days	6	Sterile × 5	15.6	7.8			
4 25 F	Chr. pyelonephritis. Diabetes	Aureomycin Chloromycetin Sulfonamide Gantrosan Penicillin	2 gm. 8 days	5	Sterile × 5	125	>62.5	>62.5	>62.5	10
7 70 M	Cystitis	Aureomycin	2 gm. 7 days	2	Pseud.* × 2	15.6	31.2	>31.2	>31.2	
17 55 M	Chr. pyelonephritis	Aureomycin Streptomycin	2 gm. 5 days	5	Sterile × 5	62.5	15.6	>62.5	>62.5	80
19 31 F	Chr. pyelonephritis. Diabetes—one kidney	Aureomycin	2 gm. 4 days	2	Sterile × 7	62.5	62.5	>62.5	>62.5	10
20 22 M	Cystitis. Atrophic bladder	Aureomycin	2 gm. 6 days	2	Pseud. × 2	15.6	15.6			
21 42 F	Chr. pyelonephritis. One kidney	Penicillin	2 gm. 2½ days	3	Sterile × 5					

TABLE III—*Continued*

No. Age Sex	Diagnosis	Previous Therapy	Daily Dose Neomycin in Grams. Duration of Therapy	No. of Cultures Before Treatment	Cultures During and After Treatment	Sensitivities of Organisms in mcgm./ml.				Neomycin Concentration in Serum, mcgm./ml.
						Neo.	Chloro.	Aureo.	Q-19	
22 75 M	Cystitis	Aureomycin Streptomycin	2 gm. 5 days	2	Pseud.* × 1	31.2	3.9	>31.2	>31.2	1.25
23 40 F	Chr. pyelonephritis	Penicillin	2 gm. 6 days	5	Sterile × 4	31.2	>62.5			
25 67 M	Chr. pyelonephritis	None	2 gm. 4 days	2	Sterile × 1					
26 69 M	Staghorn calculi	Aureomycin Streptomycin	2 gm. 7 days	2	Proteus × 2 Pseud. × 6	7.8	>62.5	31.2	>62.5	
24 37 F	Cystitis	Aureomycin Q-19	2 gm. 3 days	1	Sterile × 1	7.8	>31.2	15.6	>62.5	
60 41 F	Chr. pyelonephritis	Aureomycin Streptomycin	2 gm. 3 days	2	Sterile × 1					
61 66 F	Cystitis	Aureomycin	1 gm. 3 days	5	Sterile × 2					
27 65 F	Cystitis	Streptomycin	1 gm. 11 days	1	Sterile × 1					
66 53 F	Cystitis	Chloromycetin	1 gm. 4 days	5	Sterile × 2	62.5				
67 54 F	Cystitis	Aureomycin Sulfadiazine	2 gm. 5 days	2	Sterile × 5	62.5		>62.5	>62.5	

* Pseud. = *Pseudomonas aeruginosa.*

but no claim is being made that neomycin in the majority of cases will "cure" chronic urinary tract infections.

Preliminary in vitro experiments had indicated neomycin to be perhaps the most effective antibiotic against *Proteus vulgaris*,[2, 4, 10] so a particular effort was made to treat infections due to this organism. Seventeen patients who had proteus cultured from their urine on one or more occasions were given neomycin for periods ranging from three to eight days (table 3). In 13 cases the urine was sterilized, in three *P. aeruginosa* was subsequently isolated, and in one the proteus organisms persisted. This latter patient had bilateral ureteral catheters in place and was incontinent, so the chances for reinfection were considerable. Twelve of these patients had received aureomycin prior to therapy with neomycin. Several of the cases are presented in some detail.

Case Reports

Case 4. The patient was a 25 year old diabetic female who began having recurrent chills and fever six months before admission. She was seen at another hospital, where *Proteus vulgaris* was cultured from her urine. Following treatment with aureomycin, chloramphenicol, sulfadiazine, gantrosan, and penicillin, she continued to have chills and fever, and cultures of her urine continually demonstrated proteus. Retrograde pyelography and other renal studies had revealed no intrinsic pathology. During this period her diabetes remained out of control and there were frequent episodes of diabetic acidosis. When the patient was transferred to the University Hospitals, she was acutely ill with a fever of 103° F. She had diabetic acidosis, and complained of a severe pain in her flanks. Since it was known that the patient had had a persistent urinary tract infection due to proteus, she was given neomycin in addition to the usual measures for diabetic acidosis. Her urine did not become sterile until after 64 hours in the hospital, during which time she remained acutely ill and her fever remained at 103° F. Her diabetes was extremely difficult to control. Concomitant with sterilization of her urine she improved subjectively. The temperature returned to normal, the diabetes was controlled, the pyuria disappeared, and the pain in her flanks remitted. She made an uneventful recovery and her urine remained sterile when cultured two months after discharge from the hospital. Kidney function tests, audiograms, and vestibular functional tests done two months after discharge were normal. Of additional interest was the fact that her insulin requirement dropped to less than half of what it had been prior to her hospitalization.

Case 3. The patient was a 32 year old male whose left kidney had been removed four years prior to admission because of a "chronic infection." He entered the hospital because of intermittent chills and fever of one year's duration. His out-patient record revealed that proteus had been cultured on five occasions from his urine during this time. He was given neomycin for five and one-half days and his symptoms abated as soon as his urine became sterile. He was asymptomatic for six weeks, when he again began to have chills and fever. A culture of urine at this time showed *P. aeruginosa*, and he was readmitted to the hospital. He was given another antibiotic known as Q–19,* which failed to sterilize his urine. Neomycin was administered for the second time. The patient once more became asymptomatic at the same

* Q–19 has also been referred to as circulin. It is different from the antibiotic described by McLeod (J. Bact. **56**: 749, 1948; Ibid **58**: 115, 1949), which was originally named circulin but has since been renamed polypetin.

time that his urine became sterile. He remained well for two months, when his local physician informed us that paracolon bacilli were isolated from his urine and he had a return of symptoms. Therapy with aureomycin was then advised.

Case 17. The patient was a 55 year old white male who had suffered from chronic pyelonephritis for 10 years prior to admission. He had been subjected to all known treatments for urinary tract infections during that period, but he had never been entirely asymptomatic nor had his urine been sterile. Hematuria had been an intermittent feature of his disease. Tuberculous nephritis had been ruled out by repeated cultures and guinea pig inoculations. Retrograde pyelograms had revealed changes consistent with chronic pyelonephritis. At the time of transfer to the University Hospitals the patient was acutely ill and had a temperature that spiked daily to 104° F. *Pseudomonas aeruginosa* was cultured from his urine and the antibiotic Q–19 was given intravenously. This evoked an immediate response, which included a return to normal temperature and the disappearance of hematuria. However, subsequent urine cultures revealed *Proteus vulgaris,* so a course of neomycin therapy was given. This sterilized his urine and he was discharged. The patient remained asymptomatic until just before his follow-up visit a month later. At this time proteus was again cultured from the urine. After oral treatment with neomycin and chloramphenicol was unsuccessful in eradicating this infection, neomycin was given intramuscularly. After this therapy the urine cultures no longer grew proteus but *P. aeruginosa* appeared. To combat this organism Q–19 was given for the second time, but this only resulted in a repetition of events, i.e., the *P. aeruginosa* disappeared but subsequent cultures grew *Proteus vulgaris.* Since by this time neomycin toxicity in the form of eighth nerve damage had manifested itself, the patient was discharged asymptomatic but proteus organisms persisted in cultures of his urine.

The two preceding cases are illustrative of the fact that, while antibiotics are useful in managing chronic urinary tract infections, in many cases they do not effect a definite cure.

Eleven patients who had *Pseudomonas aeruginosa* cultured from their urine on from one to seven occasions prior to therapy were given neomycin. In eight instances this treatment was associated with sterilization of the urine. One of these patients (Case 39) was of particular interest because during the four years prior to neomycin therapy he had had 40 urine cultures, each one of which contained either *E. coli, P. aeruginosa, A. aerogenes,* or *Proteus vulgaris.* The five sterile cultures obtained after treatment with neomycin were the first ever recorded on the hospital chart in spite of previous therapy with aureomycin, streptomycin, sulfadiazine, and penicillin. Two of the seven cases did not respond to neomycin, and since *P. aeruginosa* appeared in the urine of four of 17 patients who were being treated for proteus infections, it does not appear that neomycin will be as effective against *P. aeruginosa* as against the proteus species. This was suggested on the basis of previous in vitro studies.

Four patients with urinary tract infections due to *E. coli* were successfully treated with neomycin. In the one instance in which the serum concentration of neomycin was correlated with the sensitivity of the organism to neomycin, the serum concentration was 20 mcgm./ml., and the organisms were inhibited by 31.2 mcgm./ml. of neomycin.

Eight patients with urinary tract infections due to *A. aerogenes* were treated with neomycin. In all eight instances the urine became sterile, in one *P. aeruginosa* appeared, and in another gamma streptococci were cultured from the urine. One case was particularly noteworthy in that the six sterile cultures obtained after neomycin therapy were the first in which gram-negative bacilli had not been obtained in a six-year period during which time numerous available antibiotics had been given to this patient in a vain attempt to sterilize the urine and alleviate symptoms due to chronic pyelonephritis.

Effect of Neomycin on pH of the Urine. Since Waksman [1] had found that neomycin has increased activity in basic solution, the data on the urine pH of 32 patients were analyzed. It was found that one-half of these individuals had acid urines and one-half alkaline urines prior to therapy. Ten of the 16 patients with acid urines prior to therapy had basic urine after therapy, and eight of 16 patients with basic urines before therapy had acid urines after therapy with neomycin. No relationship between therapeutic results and urine pH was found. In order to test this further, neomycin was dissolved in a series of sterile urine specimens taken from a patient who had been given sodium bicarbonate in order to raise the pH of his urine. The neomycin dissolved in urine of pH 8 was no more bactericidal than that dissolved in urine of pH 4.

3. *Bacteremia Due to Gram-Negative Bacilli.* Three patients acutely ill with bacteremia caused by gram-negative bacilli were treated with neomycin. In two, proteus organisms were the infecting agents, and in one *A. aerogenes* was cultured from the blood.

Case Reports

Case 18. The patient was a 93 year old white male who entered the University Hospitals for a transurethral resection of his prostate gland. He withstood the procedure well, but as a prophylactic measure he was given 2 gm. of aureomycin orally per day. On the fourth postoperative day, *Proteus vulgaris* was cultured from his blood and urine. He did not appear acutely ill until the seventeenth postoperative day, when he began to run a high fever. When seen on the nineteenth postoperative day, he appeared moribund and was in shock. The blood pressure could not be obtained, and his temperature was 103° F. A blood culture at this time yielded proteus. Neomycin in a dosage of two grams per day was started immediately, and within 24 hours after the start of therapy the patient was up in a chair, his temperature and blood pressure were normal, and his blood was sterile. The further hospital course was uneventful, and after six days of therapy with neomycin the patient was discharged. The organism isolated from his blood was inhibited by 15.6 mcgm./ml. of neomycin and 31.2 mcgm./ml. of chloramphenicol, but grew in 125 mcgm./ml. of aureomycin.

Case 63. The patient was a 66 year old male who was given neomycin because of a persistent bacteremia due to *Proteus vulgaris*. He was in coma because of multiple cerebral thromboses. Sterilization of the blood followed therapy, but as soon as renal toxicity forced the discontinuance of the neomycin, *Proteus morganii* appeared

in the blood. Other than the sterile blood cultures obtained during therapy with neomycin, there was no evidence of clinical response to this medication.

Case 36. The patient was a 60 year old white female who entered the University Hospitals because of recurrent severe shaking chills and fever of four years' duration. During this time she had been empirically treated with aureomycin, chloramphenicol, penicillin, streptomycin, and sulfadiazine. Two blood cultures taken soon after admission showed *A. aerogenes.* Therapy with intramuscular neomycin was started and continued with a daily dose of 2 gm. for seven days. In spite of this, her fever spiked to 102° or 103° F. each day and she continued to have shaking chills. At the completion of the neomycin therapy *A. aerogenes* was again cultured from her blood. One gram of aureomycin per day then was given by the intravenous route over a 15 day period, and a gradual improvement was noted. Her temperature became normal and her blood cultures remained sterile. This response was of particular interest because aureomycin administered orally had had no effect. When seen six months later the patient had no complaints and had gained considerable weight. The focus for her bacteremia remained unknown. The *A. aerogenes* cultured from her blood grew in 125 mcgm./ml. of both neomycin and aureomycin, but the only satisfactory response followed the aureomycin given by the intravenous route.

4. *Staphylococcic Infections.* Two patients with long standing sepsis due to coagulase-positive staphylococci were treated with neomycin.

Case Reports

Case 64. The patient was a 28 year old male who entered the hospital because of infected leukemic infiltrations of the skin which resembled large furuncles. Coagulase-positive staphylococci had been cultured consistently from the lesions for eight months prior to admission. At the onset of his infection there had been some response to intermittent therapy with aureomycin. However, the organisms cultured at the time of the present admission were resistant in vitro to penicillin, aureomycin, streptomycin, chloramphenicol, and terramycin, all of which he had received in the past. Treatment with neomycin was instituted when it was found that the staphylococci from his wounds were inhibited by a concentration of 1.9 mcgm./ml. He received neomycin for seven days, and after three days of treatment cultures of the lesions no longer revealed any staphylococci. Coincident with control of the local infection there was some improvement in his general condition.

Case 34. The patient was a three year old child with abscesses due to coagulase-positive staphylococci in his liver and over his entire body. He had received extensive therapy with aureomycin, streptomycin, and penicillin, with no improvement being noted. Thirteen grams of neomycin given over an 18 day period had no beneficial effect. Growth of the coagulase-positive staphylococci isolated from one of his lesions was inhibited by 15.6 mcgm./ml. of neomycin.

5. *Effect of Neomycin upon Proteus Morganii in the Feces.* When neomycin was given parenterally to a patient having *Proteus morganii* predominantly in the stool cultures, this species rapidly disappeared from the feces within 24 hours, but reappeared promptly when therapy was discontinued.

6. *Chronic Pulmonary Disease.* Seven patients with chronic bronchitis or bronchiectasis were treated with a combination of neomycin and penicillin. The dosage used was 0.5 gm. of neomycin given intramuscularly twice daily.

and 300,000 units of crystalline penicillin given intramuscularly once a day. The drugs were given for five to seven days. Six of the seven patients stated that they felt better after therapy and that the amount of sputum brought up each day had markedly decreased. No evidence of toxicity was noted.

7. Peritonitis with Proteus Organisms as the Predominant Bacteria. Two cases of peritonitis in which the predominant organism was *Proteus vulgaris* were treated with neomycin.

Case Reports

Case 62. The patient was a 49 year old white woman who entered the University Hospitals several weeks after the rupture of her appendix. Despite treatment with penicillin, dihydrostreptomycin, intravenous aureomycin, and two operations in which abdominal abscesses were drained, she continued to manifest a high fever and appeared moribund. Since *Proteus vulgaris* was the predominant organism cultured from draining abdominal sinuses, neomycin therapy was instituted. A daily dose of two grams was given intramuscularly for five days. During this time her fever continued to elevate to 101° F. or 102° F. daily. The neomycin was omitted because of a rise in blood urea nitrogen concentration, but at the completion of the five day course of therapy the patient's temperature returned to normal and drainage from the abdominal sinuses ceased. The white blood cell count was 27,000 at the beginning of therapy and fell to 12,000 at the time neomycin was stopped. The patient remained afebrile and continued to show improvement 10 days after neomycin had been discontinued. She was transferred to a convalescent home.

Case 27. The patient was a 65 year old woman who entered the hospital following an intestinal perforation. At operation the abdomen was drained of purulent fluid from which was cultured *Proteus vulgaris, A. aerogenes,* and *E. coli.* Streptomycin therapy was given for the first four hospital days and then neomycin was administered in a dose of one gram a day for 10 days. The patient gradually recovered and was transferred to a nursing home after 45 days in the hospital. Since the patient never became febrile and had a low leukocyte count throughout, the rôle of the neomycin in her recovery was not absolutely established. Three months after discharge the patient was readmitted and died from an *E. coli* bacteremia. Postmortem examination of her kidneys revealed normal architecture with no evidence of tubular damage.

8. Infections of Unknown Etiology. Three patients who had received ample trial of other antibiotics and who appeared to be dying of sepsis, the exact etiology of which was not clear, were given neomycin empirically. They all recovered, but in only one case was there satisfactory evidence that the neomycin was the deciding factor.

Oral Use of Neomycin

Large doses of neomycin were found to be well tolerated when given by the oral route. Two grams taken by mouth every six hours resulted in a concentration of neomycin in the blood of 1.25 mcgm./ml. However, since one-fourth of this dose given by the intramuscular route consistently gave a serum concentration of 10 mcgm./ml., it was apparent that the oral route was not economical. In the case detailed below, the renal status of the

patient was such that the risk of parenteral therapy was not undertaken but neomycin was tried orally.

Case Report

Case 65. The patient was a 63 year old woman who entered the hospital because of pain in the right flank of four years' duration. Repeated urine cultures during this time invariably had grown *E. coli.* Retrograde pyelography was interpreted as showing marked bilateral pyelonephritis. Kidney function tests revealed an ability to concentrate to a specific gravity of only 1.010; phenolsulfonephthalein excretion test of 25 per cent in two hours, and urea clearance of 37 per cent of normal. There was 1 plus albumin and 3 plus leukocytes in the urine.

The patient was given neomycin orally in a dose of four half-gram capsules every six hours. Urine cultures continued to grow *E. coli* for the first four days of therapy, but on the fifth day the urine was sterile. Simultaneously with sterilization of the urine, pyuria disappeared and the patient stated that for the first time in four years she felt free of flank pain. Therapy was continued for 10 days without incident. Kidney function tests at the conclusion of treatment showed no significant change. The patient was discharged with clear sterile urine and with no complaints. The concentration of neomycin in her blood was 1.25 mcgm./ml., and the *E. coli* isolated from her urine was inhibited by 31.2 mcgm./ml. of neomycin.

Failure of Neomycin-resistant Organisms To Appear During Therapy

In five cases, Proteus organisms were cultured one or more times during therapy with neomycin. In no instance was a marked increase noted in the resistance of the organism to neomycin. Thus, the results of therapy substantiated in vitro experiments in regard to the paucity of highly resistant variants to neomycin in a culture of a sensitive strain.[1, 2]

Toxicity of Neomycin

Since at the onset of this study the toxic potentialities of neomycin had not been established, each patient receiving the drug was examined every day for evidence of untoward reactions. Whenever possible, daily urinalysis, urine cultures, and blood urea nitrogen determinations were made and the intake and output of fluid were recorded. In addition, urine concentration tests, phenolsulfonephthalein excretion tests, urea clearance tests, and tests of hearing and vestibular function, white blood cell counts, and hemoglobin determinations were made at appropriate intervals. Neomycin was well tolerated in the muscle, and in no case was it necessary to discontinue therapy because of reactions at the site of injection. However, definite evidence of a nephrotoxic and ototoxic action of neomycin was found.

Nephrotoxic Action of Neomycin. The consistent evidence that neomycin had an irritative effect on the kidneys was the appearance of fine granular casts in the urine. Twenty-four of 32 patients in whom serial urinalyses were performed showed fine granular casts in their urine either during or just after neomycin therapy. This invariably was a transient

phenomenon, with the casts disappearing within several days after neomycin was discontinued. In this same group of 31 patients, six of the nine who had no albuminuria recorded prior to therapy with neomycin developed a trace to one plus albuminuria during or immediately after treatment. As in the case of the granular casts, albuminuria was a transient finding and disappeared within one week to 10 days after therapy was stopped. The patients who had a trace to one plus albuminuria prior to treatment did not have in any instance a marked increase in their proteinuria following therapy. No cases of hematuria attributable to neomycin were observed.

While there was a marked decrease in urine output during therapy in some of the patients who had other evidences of toxic effects from neomycin, most of the patients were able to maintain or increase their output while receiving neomycin.

Serial blood urea nitrogen determinations were made on 30 patients. Sixteen of these patients had average values of less than 20 mg. per cent before therapy, and only one of this group showed a rise in urea nitrogen during or after therapy. This was one of the patients (Case 1) who suffered eighth nerve damage and whose clinical course will be presented in detail shortly. Eleven patients had average blood urea nitrogen values of between 20 and 40 mg. per cent. In only two cases (Cases 13 and 21) did the level rise more than 5 mg. per cent during or after therapy. Case 13 suffered eighth nerve damage and will be discussed below. Case 21, a woman with one kidney, apparently suffered no permanent auditory or renal effects. Three patients whose urea nitrogen levels were 40 mg. per cent or higher before therapy had a marked increase in nitrogen retention during and after therapy. One case (Case 25) developed eighth nerve deafness and will be discussed below. The other two cases (Cases 9 and 26) were followed for over two months, at which time their blood urea nitrogen levels had approached pretreatment levels. Audiograms revealed that one patient (Case 9) had normal hearing two months after therapy. Case 26 was deaf because of prolonged streptomycin administration before the neomycin was given.

There were not enough determinations of phenolsulfonephthalein excretion and urea clearance before, during, and after therapy to be significant for statistical analysis, but many phenolsulfonephthalein excretion and urea clearance tests done after therapy were normal, although the patients showed fine granular casts in the urine during treatment.

In order to determine whether previous evidence of neomycin toxicity would contraindicate further administration of the drug, Case 61, a 66 year old woman who had shown evidence of toxicity during a previous administration of the drug, was given a second course of neomycin. During the first course the patient had been acutely ill and had shown a marked rise in blood urea nitrogen to 69 mg. per cent, a decrease in output of urine, and granular casts in the urine during therapy. However, the infection had

TABLE IV

Ototoxic Effect of Neomycin—Correlated with Renal Studies

Case No. Age Sex Diagnosis	Daily Dose of Neomycin in Grams	Duration of Therapy in Days	Renal Function Before Therapy	Auditory Function Before Therapy	Evidence of Toxicity During Therapy	No. of Days After Therapy Deafness Noted	Outcome
13 39 yrs. F Perinephric abscess	2	8	Specific grav. urine —1.014. Blood urea nitrogen—25 mg.	Subjectively normal	Rise B.U.N. to 45. Decrease urine output. Granular casts	7	Complete nerve deafness in 3 mo. Vestibular function diminished
25 67 yrs. M Pyelonephritis	2	4	Specific grav. urine —1.006. Blood urea nitrogen—71 mg.	Subjectively normal	None	10	Complete nerve deafness in 3 mo. Vestibular function diminished
1 59 yrs. F Pyelonephritis	1.5	7	Specific grav. urine —1.015. Blood urea nitrogen—18 mg.	Normal audiogram	Rise B.U.N. to 30. Granular casts. Decrease urine output	Audiogram change in 10 days	No complaints. Audiogram 3 mo. shows increasing loss of high tone perception. Vestibular function intact.
17 55 yrs. M Pyelonephritis	2 2 mo. later 2	7 5	Blood urea nitrogen —23 mg. P.S.P. 55% in 2 hours	Normal audiogram	Rise B.U.N to 29. P.S.P. 24%. Granular casts. Neomycin conc. in blood 80 mcgm. /ml.	Audiogram change begun at end of first course of therapy	Monthly audiograms showed progressive hearing loss. Vestibular function lost at 4 months
67 53 yrs. M Carcinoma of bladder	1.5 2 mo. later 2	9 7	Blood urea nitrogen —12 mg. P.S.P. 70% in 2 hours	Subjectively normal. Audiogram showed high frequency deafness	Fine granular casts	Subjective complaint at end of first course of therapy. Audiogram change in three weeks	Complete nerve deafness. Vestibular function diminished. Deafness before therapy complicated evaluation

responded to the therapy, and, coincident with the marked improvement, her blood urea nitrogen and urine output had returned to normal. The second course of neomycin was given 20 days after the first administration of the drug, and the cystitis due to proteus organisms for which it was given was controlled without evidence of toxicity. At the time of discharge, phenolsulfonephthalein excretion test was 45 per cent in two hours, urine concentrations were to 1.015, blood urea nitrogen was 14 mg. per cent, and audiograms and vestibular function tests were within normal limits.

Ototoxic Effects of Neomycin. There were five cases in this series in which it appeared likely that neomycin exerted a direct toxic effect on the eighth nerve (table 4). The first patient (Case 13), who became deaf after neomycin therapy, was a 39 year old woman who was given 2 gm. per day of neomycin intramuscularly for eight days. During this time the blood urea nitrogen had risen, the urine output had decreased, and granular casts had appeared in the urine. Seven days after cessation of therapy she began to complain of difficulty in hearing, and serial audiograms revealed progressive nerve deafness with vestibular function remaining normal. This case prompted an attempt to find out if any other patients who had received neomycin had developed difficulty in hearing. It was found that Case 25, a 67 year old man with chronic uremia who had received a course of neomycin over four days, had become "hard of hearing" beginning 10 days after therapy with neomycin had been discontinued. Audiograms and vestibular functional tests on this patient revealed progressing nerve deafness and normal vestibular function. As soon as these cases were recognized, audiograms and vestibular function tests were done before therapy with neomycin and as frequently as possible during and after treatment. Three additional patients were found in whom it appeared that neomycin had caused definite damage to the auditory portion of the eighth nerve. In the last follow-up examination, two patients had lost their vestibular function in addition to ability to hear high tones.

The similarities in the four of the five cases who suffered ototoxic effects were striking. They all had severe intrinsic renal disease, they all had either chronic nitrogen retention or a rise in blood urea nitrogen while on therapy, and in each case the first symptom or sign of ototoxic effect occurred within a week to two weeks after treatment was discontinued. The fifth case (Case 67) was treated with neomycin because of a recurrent pyelonephritis which followed repeated fulgurations of the bladder. He had no evidence of kidney disease, and the only sign of toxicity during therapy was the appearance of fine granular casts in the urine. In addition, he had difficulty in hearing high tones before therapy with neomycin was instituted. Thus, it is not absolutely certain that his deafness was caused by neomycin, but the case is included because the first symptoms occurred during treatment and complete deafness followed three weeks after the cessation of therapy. While two of the five patients still can hear, in no case has there been a

reversal of the damage revealed by serial audiograms. In each instance the auditory portion of the eighth nerve has been the first to reveal damage, although in Case 17 vestibular function was also lost.

Audiograms and vestibular function tests have been done on the majority of the other patients who have received neomycin and, except for the cases noted, no other abnormalities have been discovered.

Microscopic Examination of Kidneys of Patients Who Had Received Neomycin

Five patients who received neomycin died of their disease and sections of their kidneys were reviewed by Dr. E. T. Bell. In only one case did he find any damage that might be interpreted as having been caused by neomycin (table 5). In this case (Case 42), severe toxic tubular damage was

Table V

Correlation of Renal Toxicity Manifested during Life with the Postmortem Appearance of the Kidneys

Case No.	Age Sex	Duration of Therapy and Dose of Neomycin	Toxic Signs During Therapy	Serum Concentration, mcgm./ml.	Time Between Stopping Therapy and Death	Pathologic Findings
37	11 yrs. F	11 days; 1 gm./d. for 4 d.; 2 gm./d. for 7 d.	Granular casts; rise in blood urea nitrogen	1.5	0	Normal kidney
42	2 yrs. F	17 days; 0.75 gm./d. for 2 d.; 1.5 gm./d. for 15 d.	Granular casts; rise in blood urea nitrogen. Anuria	4.8	0	Tubular damage
27	65 yrs. F	11 days; 1 gm./d.	None		3 months	Normal kidneys
63	1 yr. M	89 days; 200 mg./d.	Granular casts; albuminuria	1.3	27 days	Normal kidneys
15	60 yrs. F	1 day; 2 gm./d.	None		0	Normal kidneys

evident and the patient died with a renal shutdown. Since promizole, streptomycin, and sulfadiazine had been administered in addition to the neomycin, it was not established that neomycin was the only offending toxic agent. Four patients had normal kidney architecture after having received neomycin for from two to 89 days, although there had been signs in the urine of a nephrotoxic action.

Discussion

The treatment with a potentially nephrotoxic drug of a group of 63 patients, many of whom were over 60 years of age and already had evidence of kidney disease, constitutes a severe test for that drug. Viewed in this

light, the evidence that has been presented of renal and eighth nerve damage due to neomycin may be extreme and may not contraindicate the use of this drug in lower dosage and in a more select group of patients. The fact that each of the four patients who suffered complete or partial hearing loss after neomycin therapy had severe renal disease indicates an increased danger from neomycin to patients with kidney disease, and means that the drug should not be used in the presence of renal damage except in cases where the threat of deafness is a minor consideration. It is unfortunate that neomycin attacks the auditory portion of the eighth nerve before the vestibular function. The signs of damage to the vestibular apparatus which provide a useful warning about streptomycin toxicity will be of no help in therapy with neomycin.

The uniform failure of neomycin to alter the course of tuberculosis in the seven cases in which it was tried should not cause the trial of the drug in this disease to be abandoned prematurely. In four of these cases, streptomycin and promizole, drugs that undoubtedly do have a place in the chemotherapy of tuberculosis, also were unable to change the course of events. The postmortem observation in two cases of a thick gelatinous membrane over the base of the brain from which were cultured tubercle bacilli helps to explain in part why chemotherapeutic measures failed. It seems apparent that therapy must be instituted before this membrane has a chance to form, or that some way must be found to penetrate or dissolve it. It is of interest that the organism isolated at post mortem from the child who had had neomycin for 89 days and who had a spinal fluid concentration of 1.25 mcgm./ml. of the drug was still moderately sensitive to neomycin. However, since increased resistance to streptomycin is not often found in organisms isolated from the theca, this cannot be accepted as final evidence that increased resistance of tubercle bacilli to neomycin will not be found subsequently. It would appear from the failure of neomycin alone to affect tuberculosis beneficially that the next avenue of investigation would be to use it in more chronic cases in small doses combined with streptomycin for the express purpose of destroying streptomycin-resistant variants as they occur.

It was predicted, on the basis of in vitro experiments, that neomycin would be effective against most strains of gram-negative bacilli and that the appearance of neomycin-resistant variants would not constitute a clinical problem.[1, 2] The clinical investigation reported in this paper was planned on the basis of these in vitro experiments and, in the main, has corroborated conclusions derived from them. Thus, while in vitro experiments do not establish the true efficacy of a new drug, the foregoing is an example of their usefulness as a prelude to clinical study.

The increasing frequency of infections due to proteus organisms and *P. aeruginosa* makes particularly important the fact that neomycin exhibited a definite beneficial effect on infections due to these organisms. These cases may be the forerunners of a host of infections that will be caused by organ-

isms that can survive the combined actions of our present antibacterial agents. This possibility should act as a stimulus to the search for drugs that will combat microörganisms still not favorably affected by available chemotherapeutic agents. In the group of cases reported in this paper, there have been some that have responded favorably to neomycin when all other available antibiotics had failed. In view of these observations, it is unfortunate that neomycin possesses a nephrotoxic and ototoxic activity. It is encouraging that, in the four patients who received one gram of neomycin per day instead of two grams, infections due to proteus organisms were eradicated. The only evidence of toxicity was the appearance of granular casts in the urine.

Summary

A clinical investigation of neomycin therapy in 63 patients has been presented. Neomycin did not exert a demonstrable effect on the seven cases of tuberculosis that were treated. Infections due to proteus organisms and to other gram-negative bacilli were favorably affected by this antibiotic. In no instance did neomycin-resistant variants appear during the course of treatment. Demonstrable levels of neomycin were present in the serum, pleural fluid, and spinal fluid of many of the patients studied. In the doses used, neomycin undoubtedly caused kidney and eighth nerve damage to a not insignificant number of patients. In view of the ototoxic and nephrotoxic effects of neomycin, this drug cannot be recommended for general use.

BIBLIOGRAPHY

1. Waksman, S. H., and Lechevalier, H. A.: Neomycin, a new antibiotic active against streptomycin resistant bacteria, including tuberculosis organisms, Science **109**: 305, 1949.
2. Waisbren, B. A., and Spink, W. W.: Comparative activity of Q-19, neomycin, aureomycin, polymyxin B and chloromycetin against gram negative bacilli, Proc. Soc. Exper. Biol. and Med. **74**: 35–40 (May) 1950.
3. Waksman, S. A., Hutchinson, D., and Katz, E.: Neomycin activity upon *Mycobacterium tuberculosis* and other mycobacteria, Am. Rev. Tuberc. **60**: 78, 1949.
4. Warth, P. T., Chandler, C. A., and Bliss, E. A.: The antibacterial action of neomycin and furadroxyl in vitro and in vivo, Bull. Johns Hopkins Hosp. **86**: 169, 1950.
5. Waksman, S. A., Lechevalier, H. H., and Harris, D. F.: Neomycin—production and antibiotic properties, J. Clin. Investigation **28**: 934, 1949.
6. Colingsworth, D. R., and Johnson, L. E.: Personal communication, 1950.
7. Karlson, A. G.: Personal communication, 1950.
8. Rake, G.: The streptomycins and neomycin in murine tuberculosis, Ann. New York Acad. Sc. **52**: 765, 1949.
9. Hobby, G. L., Lenert, T. F., and Dougherty, N.: The evaluation of neomycin and other antimicrobial agents of bacterial and fungal origin and substances from higher plants, Ann. New York Acad. Sc. **52**: 775, 1949.
10. Hobson, L. B., and McDermott, W.: Criteria for clinical evaluation of anti-tuberculous agents, Ann. New York Acad. Sc. **52**: 782, 1949.

INVOLVEMENT OF THE NERVOUS SYSTEM IN INFECTIOUS MONONUCLEOSIS *

By THEODORE C. BERNSTEIN, M.D., and HAROLD G. WOLFF, M.D., F.A.C.P., *New York, N. Y.*

ALTHOUGH involvement of the nervous system in patients with infectious mononucleosis has been described frequently during the past few years, its incidence has not been defined precisely. It is possible that some of the "idiopathic" acute disorders of the nervous system may be associated with infectious mononucleosis.† It seems pertinent, therefore, to consider the variety and phenomenology of such nervous system manifestations and to report a patient with meningo-encephalitis associated with infectious mononucleosis studied at the Bronx Veterans Hospital.

Cases cited from the literature have been classified as to symptom complex. In order to do this, certain criteria were arbitrarily set up and from all the reports a series of acceptable cases was selected.

In cases reported before the development of the heterophile antibody test,‡ a typical blood picture § associated with lymphadenopathy, either cervical or generalized, plus any of the protean signs and symptoms, was considered adequate for the diagnosis of infectious mononucleosis. In addition, an adequate description of mental, motor, or sensory defects was deemed necessary for inclusion in the series. From the time the heterophil antibody test came generally into use, no reported patient was included who did not have a positive test.

Of the unacceptable cases in the literature, there was one which was probably a bacterial meningitis,[18] one that was probably a meningismus,[11] four that were lacking in sufficient evidence,[8, 12, 22] and five cases of spinal fluid changes without evidence of mental, motor, or sensory defects.

REVIEW OF THE LITERATURE

In 1931 Johansen [1] described a 28 year old white male with serous meningitis. His clinical and blood pictures were typical of infectious mono-

* Received for publication December 4, 1948.

From the Department of Neurology, Veterans Administration Hospital, Bronx, New York City. Published with permission of the Chief Medical Director, Department of Medicine and Surgery of the Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

† First described in 1889 by E. Pfeiffer, in 1920 by Sprunt and Evans, and established as an entity by Tidy and Morley in 1921, and by Glanzman in 1930.[38]

‡ "Paul-Bunnell test" (1932)—significant in dilutions above 1:64.[38]

§ The red blood count and hemoglobin are within normal limits. There is a leukopenia early in the course of the disease, followed by a normal count or a leukocytosis. The differential count shows a marked increase in lymphocytes. Although there are several types of atypical cells, the classical one is about the size of a normal lymphocyte, with a lobulated nucleus containing chromatin in the form of a coarse network of heavy strands. The cytoplasm is basophilic and has a vacuolated foamy appearance.

nucleosis, although the heterophil antibody test was not then in use. The illness was heralded by the meningitis and recovery was complete. In the same year Epstein and Dameshek [2] described a 19 year old white male with a classical picture of infectious mononucleosis accompanied by meningo-encephalitis. The symptoms of nervous system involvement preceded the systemic manifestations by about a week, and there was complete recovery in 38 days.

There were 28 reports between 1931 and 1947.[1-28] These included 46 patients, 34 of whom were considered acceptable for the series (table 1). Of these, four were classified as serous meningitis, 10 as meningitis, four as encephalitis, and four as meningo-encephalitis. There were seven patients with meningitis or encephalitis followed by what appeared to be an acute polyneuronitis which was suggestive of the Guillain-Barré syndrome. There were also six patients with peripheral neuropathy. These are listed in table 2.

Typical examples of the above classification are described below:

A. Serous Meningitis. Solomons [20] described a 20 year old male who had suffered from lassitude and anorexia for a period of three weeks. Five days prior to admission to the hospital he developed severe frontal occipital headache, accompanied by slight photophobia. On admission he had a temperature of 103° F., with a pulse rate of 100. His skin was moist and hot, and his cervical lymph nodes were enlarged and tender bilaterally. There was slight nuchal rigidity, with no other evidence of mental, motor, or sensory defects. His blood picture was typical of infectious mononucleosis, and his heterophil titer in the blood was 1:2,000. Lumbar puncture showed clear fluid with a pressure over 300 mm. of water. There were no cells. The spinal fluid was otherwise normal. There was a dramatic subsidence of the severe headache with lumbar puncture, and during the first week of hospitalization two repeat punctures (for the removal of spinal fluid) were done with marked relief of symptoms. Recovery was gradual and complete.

B. Meningitis. Coogan, Martinson and Mathews [21] discussed a 23 year old female who, four days prior to admission, developed fever, headache, and aching in the legs. On admission to the hospital the patient had cervical adenopathy, a typical blood picture of infectious mononucleosis, and a heterophil antibody titer of 1:128. Examination of the nervous system showed nuchal rigidity, a bilateral Oppenheim, and a definite Babinski on the right with a suggestive one on the left. Spinal tap showed a pressure of 250 mm. of water. The fluid was clear and colorless. There were 150 cells, 85 per cent of which were lymphocytes. The total protein was 144 mg. per cent and the Pandy 3 plus. The patient recovered completely in three weeks.

C. Encephalitis. Landes, Reich and Perlow [13] described a patient with generalized lymphadenopathy, splenomegaly, a typical blood picture, and a heterophil antibody titer of 1:1,024. This patient complained of severe headache, dizziness, vomiting, and a staggering gait for one week prior to admission. At first he was irritable, but later he became lethargic and irrational. Examination on admission to the hospital showed a semistuporous patient with an expressionless face. His speech was slurred and explosive and he showed poor coördination with dysmetria. He was able to stand only on a wide base and even then with marked swaying. His gait was markedly ataxic. Lumbar puncture showed a pressure of 152 mm. of water. The fluid was clear and colorless; there were 9 cells, all lymphocytes. The total protein

TABLE I

Review of the Literature

Report	Age and Sex	Signs and Symptoms of Infect. Mono.	Incubation Period	Evidence of Nervous System Involvement	Spinal Fluid Findings	Recovery	Neurological Diagnosis
Johansen	M 28	Difficulty in swallowing, necrotic angina, cervical adenopathy (heterophil antibody not done at this time). Blood picture typical	Apparently presenting symptom	Headache, drowsiness, nuchal rigidity, impaired memory and "awkward speech"	"Marked increase in pressure," clear, 8 cells, normal protein	? Days Complete	Serous meningitis
Epstein and Dameshek	M 19	Generalized lymphadenopathy, splenomegaly, typical blood picture (heterophil antibody not done at this time)	Apparently presenting symptom	Headache, nuchal rigidity, Kernig, photophobia, blurred vision, lethargy, stupor, Oppenheim, transient Babinski, profanity, euphoria, slight ptosis rt. eye	Normal pressure, fluid clear with w.b.c.'s (90% lymph.) Protein 52 mg. %. Sugar 62 mg. %, globulin neg. Wass. neg. Coll. gold flat	Complete 42 days	Meningo-encephalitis
Fledelius	M 21	Cervical adenopathy, necrotic angina, typical blood picture (heterophil antibody not done at this time)	2 days	Headache, insomnia and restlessness. Paresis of left inferior rectus with diplopia. Knee jerks hyperactive	Clear 2 cells	Complete 2½ months	Peripheral neuropathy
Sucher and Schwarz	F 17	Generalized lymphadenopathy, splenomegaly, hepatomegaly, typical blood picture (heterophil antibody not done)	Onset unknown; relapse 20 days later	Headache, nausea, vomiting, nuchal rigidity, Kernig, eyeballs painful on pressure, Oppenheim, Babinski, decreased abdominals. Psychomotor retardation, irritability, coma, convulsions (status), opisthotonos, ataxia, adiadokokinesis, poor finger to nose, nystagmus and third nerve paresis on rt. with lt. hemiparesis (Weber's syndrome)	Increased pressure, fluid clear with pellicle formation. 100 cells (all lymphs.) Pandy 4, Wass. neg. Gold sol. 1:1,200	Complete 55 days	Meningo-encephalitis
	F 15	Generalized lymphadenopathy, splenomegaly, typical blood picture (heterophil antibody not done)	Onset unknown; relapse 10 days later	Headache, nausea, vomiting, nuchal rigidity, ataxia, diplopia, coma, convulsions (status), left hemiparesis	Increased pressure 100 cells	Complete 14 days	Meningo-encephalitis
Davidsohn	F 16	Sore throat, enlarged tender cervical nodes, ulcerative pharyngitis, typical blood picture. Heterophil antibody 1:896	16 days	Unconscious, convulsions	Clear 18 cells	? Complete	Meningitis
Gsell	M 17	Splenomegaly, hepatomegaly, generalized lymphadenopathy, typical blood picture (heterophil antibody not done)	4 days ?	Apathetic, headache, nuchal rigidity, Kernig, Babinski	Pressure 200, fluid clear 200 cells (lymphs), protein 44, sugar normal, gold curve flat	Days complete	Meningitis

TABLE I—*Continued*

Report	Age and Sex	Signs and Symptoms of Infect. Mono.	Incubation Period	Evidence of Nervous System Involvement	Spinal Fluid Findings	Recovery	Neurological Diagnosis
Gsell	M 22	Generalized lymphadenopathy, splenomegaly, typical blood picture (heterophil antibody not done)	Onset	Headache, nausea and vomiting, nuchal rigidity, Kernig, dev. "optic neuritis" on tenth day.	Pressure 170, fluid clear and colorless, 760 cells (lymphs. predom.), Pandy positive	Meningeal signs gone by 25th day, CSF not normal until 81st day	Meningitis
	M 20	Sore throat, general lymphadenopathy, splenomegaly. Typical blood picture (heterophil antibody not done)	Onset	Headache, photophobia, nuchal rigidity, Kernig	Pressure 190, fluid clear and colorless, 434 cells (lymphs, monocytes and polys.)	74 days complete	Meningitis
	M 22	General lymphadenopathy, splenomegaly. Typical blood picture (heterophil antibody not done)	21 days 28 days	Complete rt. facial Complete lt. facial	No lumbar puncture	10 comp. 7 comp.	Peripheral neuropathy
	M ?	General lymphadenopathy, splenomegaly. Typical blood picture (heterophil antibody not done)	31 days	Complete rt. facial	No lumbar puncture	7 complete	Peripheral neuropathy
Schmidt and Nyfeldt	F 16	Severe angina, "adenitis," typical blood picture, heterophil 1:128	? 3 weeks	Headache, nuchal rigidity, Kernig, Babinski	Pressure 290, fluid clear and colorless, 26 cells (lymphs.), "globulin pos." Wassermann negative. Heterophil antibody negative.	? 2 mos. complete	Meningitis
	F 18	Sore throat, gen. lymphadenopathy, typical blood picture. Heterophil antibody 1:256	—	None	Pressure 300, fluid clear 10 cells, albumin, globulin negative, heterophil antibody negative	—	Cerebrospinal fluid changes without neurological signs
	M 24	Sore throat, gen. lymphadenopathy, typical blood picture. Heterophil antibody 1:512	—	None	53 cells, albumin slightly increased	—	Cerebrospinal fluid changes without neurological signs
	M 14	Sore throat, adenitis, typical blood picture, heterophil antibody 1:56	—	None	29 cells, albumin slightly increased	—	Cerebrospinal fluid changes without neurological signs
	F 23	Sore throat, adenitis. Blood picture 65% mononuclears. Heterophil antibody negative	—	None	18 cells, albumin slightly increased	—	Not acceptable because of insufficient evidence

TABLE I—*Continued*

Report	Age and Sex	Signs and Symptoms of Infect. Mono.	Incubation Period	Evidence of Nervous System Involvement	Spinal Fluid Findings	Recovery	Neurological Diagnosis
Huber	M 26	Pharyngitis, gen. lymphadenopathy, splenomegaly, typical blood picture, heterophil antibody "positive"	1 week	Headache, insomnia, clouded sensorium, nuchal rigidity, Lasègue, Kernig, hyperesthesia up to knees bilaterally accompanied by pain and pseudo paralysis, knee jerks faint	Pressure 350 cells (mostly mononuclears), total protein 77, sugar, chlorides neg., third zone gold curve, later 1000 cells (mostly lymphs.)	14 days complete	Meningitis and peripheral neuritis
Pietzonka	M 28	Gen. lymphadenopathy, splenomegaly, hepatomegaly, typical blood picture, heterophil antibody 1:64	1 week	Headache, nuchal rigidity, Kernig, mild opisthotonos, apathetic, poor contact, papilledema	Pressure 420, fluid clear and colorless, 95 cells (lymphs.), Pandy pos., sugar and chlorides pos., Wass. neg.	2 weeks complete	Meningitis
	M 20	Gen. lymphadenopathy, splenomegaly, hepatomegaly, typical blood picture, heterophil antibody 1:64	Onset	Headache, slight nuchal rigidity	Pressure 350, fluid clear and colorless, 6 cells, sugar and chlorides neg., total protein 26	2 weeks complete	Serous meningitis
	M ?	Gen. lymphadenopathy, splenomegaly, hepatomegaly, typical blood picture, heterophil antibody 1:64	Onset	Headache, slight nuchal rigidity	Pressure 460, fluid clear and colorless, 9 cells, otherwise neg.	3 weeks complete	Serous meningitis
Marshall	M 29	Sore throat, cervical adenopathy, typical blood picture, heterophil antibody 1:512	10 days	Headache, nuchal rigidity, photophobia, "could not articulate well," "horizontal nystagmus"	Pressure not given, fluid clear, no cells, gold curve flat, Kline neg.	?	Meningismus
Thelander and Shaw	F 22	Gen. lymphadenopathy, splenomegaly, typical blood picture, heterophil antibody 1:160	13 days prior to gen. signs	Headache, nuchal rigidity	Pressure not given, fluid clear, 630 cells (70% lymphs.), gold curve flat, "others neg."	? Cerebrospinal fluid still showed 82 lymphs. after 4 mos. comp.	Meningitis
	F 3½	No adenopathy, no splenomegaly, increase in lymphocytes in blood, heterophil antibody negative	?	"Convulsion"	40 lymphocytes	?	Unacceptable because of insufficient evidence
	F 2½	No adenopathy, no splenomegaly, increase in lymphocytes in blood, heterophil antibody negative	?	Muscular twitching	70 lymphocytes	?	Unacceptable because of insufficient evidence
Landes, Reich and Perlow	M 21	Gen. lymphadenopathy, splenomegaly, typical blood picture, heterophil antibody 1:1024	Dev. gen. signs 19 days after onset	Headache, vertigo, vomiting, lethargy, stupor, catatonia, irrationality, speech slurred and explosive, ataxia, dysmetria	Pressure 152, clear, 9 lymphocytes, total protein 170, sugar 46, Pandy 1, Wass. neg., gold curve flat, heterophil antibody neg.	?	Encephalitis

TABLE I—*Continued*

Report	Age and Sex	Signs and Symptoms of Infect. Mono.	Incubation Period	Evidence of Nervous System Involvement	Spinal Fluid Findings	Recovery	Neurological Diagnosis
Richardson	M 26	Severe sore throat, cervical adenitis, typical blood picture, heterophil antibody "strongly positive"	21 days	Aching over right shoulder, followed by incomplete paralysis of serratus anterior on right	Not reported	?	Peripheral neuropathy
Zohman and Silverman	M 21	Gen. lymphadenopathy, typical blood picture, heterophil antibody 1:1024	21 days	Headache, nuchal rigidity, irritability, irrationality, myoclonic and athetoid movements, flaccid paralysis of all extremities with absence of all deep reflexes plus occasional fasciculations, able to move only fingers and toes. Gen. pains in extremities, and back particularly, marked tremors and perspiration, difficulty voiding, ptosis rt. lid, lt. peripheral facial paralysis, speech drawling and nasal	Pressure 130, clear and colorless, 4 cells, 4 albumin, slight globulin	? Had motor weakness, atrophy and moderate left foot drop	Meningo-encephalitis followed by an acute polyneuronitis (suggestive of Guillain-Barré syndrome)
Leavell and McNeel	M 29	Typical blood picture, heterophil "positive"	3 days ?	Headache, drowsiness, aroused with difficulty, neurological examination repeatedly negative	Pressure not given, clear, 26 cells (lymphs.), sugar neg., globulin increased, chlorides neg.	? 2 wks. later 24 cells	Encephalitis
Hiller and Fox	M 17	Gen. lymphadenopathy, splenomegaly, typical blood picture, heterophil antibody 1:256	? 2–3 weeks for meningeal signs—flaccid paralysis 5 days later	Nuchal rigidity, Kernig, Brudzinski, diplopia, rt. facial weakness, "difficulty in speech," diff. in swallowing, complete flaccid paralysis, absence of reflexes, unable to have bowel movements	2 white blood cells, protein 360, globulin + "heavy," sugar 63, chlorides 731, colloidal gold curve flat	Approx. 1 month	Meningitis followed by acute polyneuronitis (suggestive of Guillain-Barré)
Saksena	M 25	Sore throat, gen. lymphadenopathy, rash, splenomegaly, typical blood picture, heterophil antibody 1:900	11 days	Severe pain in rt. shoulder followed by severe paralysis of serratus anterior	Pressure normal, clear, no cells, total protein 45	50% loss of function 2 mos. later	Peripheral neuropathy
Shafer and Weir	M 28	Gen. body aches, malaise, sore throat, lymphadenopathy, blood picture not typical, heterophil antibody negative	5 days	Headache, nuchal rigidity, photophobia, Kernig	Milky fluid with purulent deposit, cells "increased" —87% polys., protein elevated	4 days after sulfa	Not acceptable (probably a pyogenic meningitis)
Solomons	M 20	Tender, enlarged cervical glands, typical blood picture, heterophil antibody 1:2,000	16 days	Headache, photophobia, blurring of vision, lethargy, impaired memory	Pressure "over 300," no cells, gold curve flat	Approx. 1 month	Serous meningitis
Coogan, Martinson, and Mathews	F 22	Cervical adenopathy, typical blood picture, heterophil antibody 1:128	4 days	Headache, nuchal rigidity, bilateral Oppenheim, positive Babinski rt., suggestive left	Pressure 250, clear, colorless, 150 cells, (85% lymphs.) Ross Jones 2+, Pandy 3+, total protein 144	4 weeks complete	Meningitis

TABLE I—*Continued*

Report	Age and Sex	Signs and Symptoms of Infect. Mono.	Incubation Period	Evidence of Nervous System Involvement	Spinal Fluid Findings	Recovery	Neurological Diagnosis
Coogan, Martinson, and Mathews	M 24	Sore throat, typical blood picture, heterophil antibody 1:2,048	10 days	Pain down both arms with weakness and inability to move left arm away from side; definite atrophy of deltoid and muscles of shoulder group	6 cells, Pandy 4+, Ross Jones 3+, total protein 100	8 weeks complete	Acute polyneuronitis (Guillain-Barré)
	M 31	Headache, lassitude, typical blood picture, heterophil 1:1,024	5 days	Headache (?)	Pressure 300, 4 cells, Ross Jones 2+, Pandy 3+, total protein, 80	2 weeks	Spinal fluid changes without neurological signs
	F 24	Sore throat, typical blood picture, heterophil antibody "pos."	7 days	Headache (?)	Pressure 110, no cells, Ross Jones neg., Pandy 1+, protein 30	?	Spinal fluid changes without neurological signs
Geliebter	F 10	Cervical adenopathy, typical blood picture, heterophil antibody 1:256	28 days	Headache, nuchal rigidity, Kernig, pain in both hips and shoulders, general weakness of all muscle groups, inability to sit up without support, all deep reflexes diminished to absent, hyperesthesia, transient diplopia	Pressure "increased," fluid clear, 9 lymphs., 6 red blood cells, total protein 400, "large" excess globulin, chlorides 740, sterile	51 days complete	Meningitis followed by acute polyneuronitis (suggestive of Guil'ain-Barré syndrome)
Slade	M 31	Gen. lymphadenopathy, typical blood picture, heterophil antibody 1:896	11 days	Headache, sucking and smacking movements of the lips, cog-wheel rigidity, ataxia, adiadokokinesis, athetoid movements, gen. muscular weakness, marked weakness of trapezius and sternomastoid, compl. bilateral facial paralysis, loss of gag reflex, paralysis of upward gaze, loss of convergence, loss of taste ant. 1/3 tongue, loss of pain, temp. and light, touch and vibration over face, rt. abdominals sluggish, rt. cremasteric absent. EEG consistent with diffuse encephalopathy	4 cells, total protein 91, heterophil antibody neg.	200 days incomp., still had some bilateral facial weakness and numbness	Encephalitis
	M 36	Gen. lymphadenopathy, typical blood picture, heterophil antibody 1:112	17 days	Headache, bilateral facial hyperesthesia over temporo-mandibular region and anesthesia of chin, dysarthria, absence of gag, paresis of masseters and pterigoids, increased aching of extremities, gen. muscular tenderness, and weakness, adiadokokinesis, diminished to absent deep reflexes, diminished superficial abdominals and cremasters with neg. plantar response, rt. foot drop	2 cells, total protein 48 total protein 48	150 days incomplete weakness, diminished deep reflexes, slight facial weakness persisted	Encephalitis accompanied by acute polyneuronitis (suggestive of Guillain-Barré syndrome)
Wechsler, Rosenblum, and Sills	M 24	Follicular tonsillitis, generalized lymphadenopathy, typical blood picture, heterophil antibody 1:224	8 days	Headache, hyperirritability, nuchal rigidity, "slight haziness of disc borders"	524 w.b.c. (517 lympha.), globulin 4+, sugar 104, chlorides 540, coll. gold neg., Wass. neg.	Still showed cells on 60th day—no signs	Meningitis

TABLE I—*Continued*

Report	Age and Sex	Signs and Symptoms of Infect. Mono.	Incubation Period	Evidence of Nervous System Involvement	Spinal Fluid Findings	Recovery	Neurological Diagnosis
	M 29	Sore throat, cervical adenopathy, splenomegaly, typ. blood picture, heterophil antibody 1:1,792	7 days	"Brachial neuritis"	No tap	14 days	Not acceptable because of insufficient evidence
Vaughn et al.	M 38	Gen. lymphadenopathy, typical blood picture, heterophil antibody 1:1,280	?	Headache, nuchal rigidity, paralysis left external rectus with diplopia, bilateral ankle clonus—all reflexes exaggerated	Pressure 175, 8 cells, protein 116, sugar 136, gold curve flat	Complete 44 days	Meningo-encephalitis
Schneider and Michaelson	M 18	Gen. lymphadenopathy, splenomegaly, typical blood picture, heterophil antibody 1:28,000	5 days	Headache, stuporous, delirious, restless, all limbs spastic, brisk reflexes, rt. Babinski, euphoria	Pressure 240, 4 polys. (?) sl. excess glob., chlorides 695, sugar 55, gold curve negative, heterophil antibody neg.	Incomplete poor concentration, possible mild aphasia of motor type	Encephalitis
Ashworth and Motto [8]	M 19	Splenomegaly, typical blood picture, heterophil antibody 1:448	?	Bilateral papilledema, pupils not described, visual acuity and visual fields not described, no neural signs	Pressure 125, clear—1 cell, protein 38, sugar 52, chlorides 670	31 days comp.	Optic neuritis (not acceptable because of insufficient evid.)
Wickers et al.	M 22	Cervical adenitis, typical blood picture, heterophil antibody 1:1,792. Autopsy: evidence of infectious mononucleosis	12 days	Headache, nuchal rigidity, tingling and numbness of hands and feet with rt. peripheral facial paralysis, mod. depressed gag, some difficulty in swallowing, hyperesthesia of hands and feet, flaccid paralysis of all extremities accompanied by absence of all deep reflexes, respiratory paralysis, convulsions and death	36 cells (94% lympha.) total protein 81	Death	Meningitis followed by acute polyneuronitis (suggestive of Guillain-Barré syndrome)
	M 21	Cervical adenitis, suggestive blood picture, heterophil antibody not done. Autopsy: evidence of infectious mononucleosis	18 days	Soreness and weakness of lower extremities, weak intercostal action in lower third, definite weakness of upper extremities and paralysis of trunk and lower extremities, transient paresthesias of feet, hands and legs, no sensation loss, all deep and abdominals absent, respiratory paralysis and death	8 cells, total protein 74, sugar 50, chlorides 627	Death	Acute polyneuronitis (Guillain-Barré syndrome)

was 170 mg. per cent. Three days following admission the patient began to improve and recovery was complete.

D. Acute Polyneuronitis. Zohman and Silverman [18] presented a 21 year old white male who, three weeks prior to admission, developed headache, weakness, and fever. These symptoms persisted, the patient became very irritable, and on the day prior to admission he awoke to find that he was unable to move his extremities. Physical examination on admission revealed cervical, submaxillary, and axillary adenopathy. The blood picture was characteristic of infectious mononucleosis and the heterophil titer was 1:1,024. Neurologic examination showed ptosis of the right upper eyelid, a left complete facial paralysis, slight nuchal rigidity, and an almost complete flaccid paralysis of all his extremities. The patient was able to move only his fingers and toes. There were some "fibrillatory" twitches of the right arm without any noticeable atrophy. All the deep reflexes were absent. There were no sensory disturbances. Lumbar puncture showed clear fluid with 4 cells. Albumin was reported as "4 plus." The patient had great difficulty in voiding and slight difficulty in swallowing. He had severe pain in all the muscles, mostly in the back and upper extremities. He also exhibited marked generalized tremors, and he perspired profusely. His speech became drawling and nasal. At times the patient became irrational. Improvement began after one week, but at the time of the report he still had generalized motor weakness, some atrophy, and a moderate left foot drop.

TABLE II

Classification of Acceptable Cases

Diagnosis	Number
Serous meningitis	4
Meningitis	10
Encephalitis	4*
Meningo-encephalitis	4
Meningitis or meningo-encephalitis with acute polyneuronitis	7
Peripheral neuropathy	6†

* Not including case reported here.
† One of these cases also included in meningitis group.

This patient had signs of meningo-encephalitis, accompanied by other nervous system signs which could be classified as an acute polyneuronitis. These latter manifestations, plus increased protein in the spinal fluid without concomitant pleocytosis (albuminocytologic dissociation), are suggestive of the Guillain-Barré syndrome.

E. Peripheral Neuropathy. Saksena [19] described a 25 year old white male with generalized lymphadenopathy, splenomegaly, typical blood picture, and a heterophil titer of 1:900, who on the eleventh day of his illness developed severe pain in his right shoulder followed by paralysis of the right serratus anterior. Lumbar puncture revealed normal pressure. The fluid was clear and colorless, without cells, and the total protein was 45 mg. per cent. Two months later the patient still had winging of the right scapula, with about 50 per cent loss of function.

Ashworth and Motto [28] have described a patient with infectious mononucleosis complicated by bilateral papilloretinal edema. This 19 year old white male had edema of the optic disc, but had a normal spinal fluid (including pressure) and no evidence of mental, motor, or sensory defects. Unfortunately, the pupils and their reaction to light are not described, nor

was there any report of visual acuity or peripheral fields. The existence of bilateral optic nerve edema in the absence of an increased spinal fluid pressure makes it more likely that the patient had an optic neuritis than papilledema. Gsell [8] reported a patient with meningitis accompanied by "optic neuritis." Here the spinal fluid pressure was normal. Again, unfortunately, there was no adequate description of pupils, acuity, or fields. Pietzonka [9] described a young man with meningitis accompanied by a marked increase in spinal fluid pressure and what was described as papilledema. Again, pupils, acuity, and fields were not described. It is known that papilledema may occur with a meningeal infection accompanied by increased intracranial pressure. This would occur regardless of the etiology. The presence of optic neuritis with infectious mononucleosis, however, is of much greater interest. This pathologic process has been described with other infectious diseases. Although the patient described by Ashworth and Motto probably did have optic neuritis associated with infectious mononucleosis, it is unfortunate that he cannot be included in the series because of insufficient evidence.

Meningo-encephalitis may result from invasion of the nervous system by many agents. In many instances, specific viruses have been isolated and described. More often, attempts at identifying the etiologic agent have been unsuccessful.

A report follows of a patient with meningo-encephalitis in the course of infectious mononucleosis studied at the Bronx Veterans Hospital.

Case Report

The patient, a 19 year old white male with no past history of disease of the nervous system, was apparently well until September 1, 1947, when he developed bifrontal headache and fatigue. These symptoms persisted for three days and were accompanied by restlessness and a feeling of being "choked up." On September 4, the patient had a rise in temperature to 102° F., fainted, and "went completely out of his head." His speech became unintelligible and he "raved through the night." He was admitted to the hospital on the following day, at which time his temperature was 97.5° F., pulse 72, respirations 20, and blood pressure 150/86 mm. Hg. Physical examination revealed a few soft axillary nodes bilaterally, but otherwise showed no abnormalities. The patient was moderately restless, disoriented as to place and approximately oriented as to time. He was unable to obey direct commands and was easily distracted by extraneous noise. There was some perseveration. There were no hallucinations, delusions, or ideas of reference. His speech was generally incoherent and irrelevant. He frequently closed his eyes and withdrew momentarily, either during conversation or performance. He complained of mild headache.

Examination of nervous system function revealed: 1. Slight resistance in flexing the neck, not accompanied by a Kernig's sign. 2. Absent superficial abdominals. 3. Slight motor aphasia. 4. Diminished perception of sensation to pin and cotton over the distribution of all divisions of the fifth cranial nerve. 5. Mild left lower facial weakness.

On the second day of hospitalization the patient was essentially the same. On the third day he seemed more alert in the morning, but again became irrational later in the day. He vomited all of his ingested food and complained of blurred vision and slight headache. A repeat examination revealed the same findings as on admission.

There was no evidence of papilledema. On the morning of the fourth day he appeared much more alert. A lumbar puncture was done at 11:30 a.m. About five minutes following the tap the patient had a generalized convulsion which began with arching of the back, severe facial twitching, and tongue biting. His head and eyes were turned to the right. The initial tonic phase was followed by severe clonic movements, more on the right side. The patient was incontinent of urine during this attack. Fifteen minutes later he had a second generalized convulsion, followed by coma. The patient was noted at this point to be very hypersensitive to touch and sound. He remained comatose for 24 hours, during which time he had repeated seizures which consisted of arching of his back, accompanied by slow, uncertain, not convulsive flexion movements of his arms and carpopedal position of the extremities. There were grunting, snorting respirations and chewing movements, with grinding of the teeth. The eyes showed dissociated movements with fluctuating pupillary size. The patient had generalized hyperreflexia, with clonus in the arms and legs and with bilateral extensor plantar responses. He had marked nuchal rigidity and a bilateral

TABLE III

Laboratory Findings in Case Report

	Date (1947)							
	9/5	9/8	9/10	9/13	9/18	9/22	9/26	10/1
Blood								
RBC (per cu. mm.)	5.0	5.1	5.1	5.2	5.2	4.7	5.2	4.8
Hb. (grams %)	17.0	17.1	17.3	17.3	17.3	16.0	17.3	15.5
W.B.C. (per cu. mm.)	8800	10,200	9400	12,000	8200	8400	7800	5400
Neutrophils %								
segmented	45	45	46	15	36	35	32	28
non-segmented	15	12	4	8	0	0	0	0
Lymphocytes %	35	37	43	62	56	53	59	62
Monocytes %	5	6	5	13	8	8	6	7
Eosinophils %	0	0	2	2	0	1	3	3
Plasma cells %	0	0	0	0	0	3	0	0
Heterophil Ab.			1:448		1:448	1:448	1:448	1:112
C.S.F.								
Pressure (mm. water)	135	170					135	112
Appearance	traum.	clear					clear	clear
Cells (per cu. mm.)	19 P 70 R.B.C.	120 (90% L)					18 Lymp	0
Sugar (mg. %)	69	60						
Protein (mg. %)	117	156					31	
Gold curve	flat	flat						
Wassermann	negative	negative						
Chlorides (mg. %)	700	700						
							negative	negative

Kernig's sign. The attitudinal reflexes were demonstrable. At the end of this 24 hour period the patient regained consciousness and appeared considerably improved. He was drowsy but responded occasionally to questions. He continued to show improvement throughout the day but the drowsiness persisted. From this point on, recovery, although slow, was progressive and complete. He was discharged as having completely recovered at the end of one month and, when seen three months later, showed no residuals of his severe illness.

On the thirteenth day of his illness the patient developed enlarged tender cervical lymph nodes. There was no angina. Later, small inguinal nodes appeared. These were the only signs of lymphadenopathy. The spleen was never palpable. The white blood count on admission was 8,800, with 60 per cent neutrophils, 35 per cent lymphocytes, and 5 per cent monocytes. During his hospitalization the patient gradually developed a predominance of mononuclear cells which at one point reached 75 per cent. The blood smear became typical of infectious mononucleosis. The heterophil antibody titer in the blood was reported as 1:448 on the fifth day of hospitalization.

Lumbar puncture on the day of admission showed an initial pressure of 135 mm. of water. The tap was traumatic. The cells were reported as 19 polymorphonuclears (?) and 70 red blood cells. The total protein was 117 mg. per cent, the sugar 69 mg. per cent, and the chlorides 700 mg. per cent. Wassermann and Kahn were negative and the gold curve was flat. A repeat lumbar puncture on the third hospital day showed an initial pressure of 170 mm. of water, with clear colorless fluid. There were 120 white blood cells, of which 90 per cent were lymphocytes. The total protein was 156 mg. per cent. All the other constituents were normal. Heterophil antibodies were not detected in the spinal fluid.

The blood and spinal fluid findings are listed in table 3. All urines were normal. The sedimentation rate was normal. No growth was obtained on either blood or spinal fluid culture. Stereoscopic roentgen-rays of the skull showed no abnormalities. Electroencephalograms showed grossly pathologic records, which reverted to normal with clinical improvement.

This, then, is an instance of meningo-encephalitis in a patient who showed minimal clinical manifestations of infectious mononucleosis, but had a typical blood picture and a positive heterophil antibody test in the blood. The midbrain appeared to be the most involved in the encephalitic process. Involvement of the nervous system preceded the mild systemic manifestations. Recovery was complete in 30 days. The entire clinical picture was indistinguishable from other forms of encephalitis.

Discussion

Etiology: In attempting to discover an infective agent for infectious mononucleosis, many microörganisms have been suspected but there has been no definite implication of any specific organism. In 1926, Murray, Webb and Swann [29] found that *Bacterium monocytogenes* was the etiologic agent for a disease of rabbits characterized by pronounced monocytosis. In 1929, Nyfeldt [30] isolated an organism called *Bacterium monocytogenes hominis* from the blood and with this organism, using rabbits, succeeded in producing the blood picture of infectious mononucleosis. Soon after, Bland [31] reported that he had produced a disease in a rabbit which closely resembled infectious mononucleosis by injecting blood from a patient suffering from the disease. He inferred that one of the species of toxoplasma was the etiologic agent. Van den Bergh and Liessens [32] reported in 1939 that they had produced a disease in monkeys resembling infectious mononucleosis. In producing this disease they used blood from a patient having infectious mononucleosis, the blood having been passed through a Berkefeld filter and cultured before injection. They stated that the animals developed a positive heterophil antibody test. However, these findings have not been confirmed. In 1939 Julianelle, Bierbaum and Moore [33] attempted unsuccessfully to transmit the disease to laboratory animals. They used blood, pharyngeal washings, and lymph node tissue. Although there was a tendency toward leukocytosis, with increase in both lymphocytes and monocytes, in no case did the leukocytes present the characteristics of those seen in patients with infectious mononucleosis. Moreover, they showed that this leukocytosis was a non-

specific response, possibly to a foreign protein. None of their animals developed a positive heterophil antibody test. In addition, attempts to transfer the disease to humans were unsuccessful.

Favoring the virus etiology of infectious mononucleosis is a report by Burnet and Anderson,[34] in which they were able to agglutinate human red blood cells sensitized by the virus of Newcastle disease with sera from patients with infectious mononucleosis. However, the concept of a virus etiology must still be confirmed.

Pathology: Because few patients come to autopsy, there have been relatively few reports of the gross pathologic histologic changes found in infectious mononucleosis. It is now believed that infectious mononucleosis is a generalized disease with organic changes as evidenced by cellular infiltration in almost every organ of the body, the clinical picture depending on the predominant site of involvement. Downey and Stasney[35] have described the pathologic picture in excised lymph nodes. They noted hyperplasia of both lymphocytes and reticulum, but never complete obliteration of the nodal architecture. Gall and Stout[36] described a similar picture in lymph nodes. In 1946, Allen and Kellner[37] described a young man with infectious mononucleosis who died in an airplane crash one month after the onset of his illness. Autopsy revealed focal areas of infiltration consisting almost exclusively of large mononuclear cells in most organs of the body. It is of extreme interest to note here that section of the brain showed that a few blood vessels in the cerebral cortex revealed a heavy cuffing of mononuclear cells, mostly lymphocytes, despite the fact that the patient did not have any symptoms of nervous system involvement.

Ricker et al.,[27] who described two patients in whom involvement of the nervous system was extensive and death resulted from respiratory paralysis, give complete autopsy reports particularly as related to the nervous system. In the first patient the leptomeninges were congested and showed occasional minute hemorrhages, and in the arachnoid there were moderate numbers of mononuclear cells. Occasional small perivascular hemorrhages were encountered in the cerebrum, most prominently in the hippocampal region. In the cerebellum, the Purkinje cells were considerably distorted, many nuclei being either indistinct or indiscernible. In the left anterior horn of the spinal cord, the motor cells showed peripheral condensation of the Nissl substance and nuclear chromatin and vacuolization of the cytoplasm. In the interfascicular perineurium, particularly related to blood vessels of the anterior nerve root, there were accumulations of small round cells, scattered larger mononuclear cells, and a few eosinophils.

In the second patient, the leptomeninges were edematous, and there were a few accumulations of lymphocytes, large mononuclear cells, and occasional neutrophils. The capillaries and small veins from all sections of the nervous system were engorged. In addition, small perivascular hemorrhages were noted in the gray matter of the lower cervical cord. The ganglion cells at all levels of the cord, as well as in the cerebral cortex, showed mild changes,

such as vacuolization, early chromatolysis, decreased affinity of the cytoplasm for eosin, and dispersal of nuclear chromatin. Occasional shrunken ganglion cells, surrounded by an increased number of oligodendroglial stellites, were noted in the cortex of the parietal lobe. Sections from the spinal nerve roots revealed marked congestion and edema of the nerve fasciculi. Cellular infiltration of the anterior nerve roots was noted at all levels but was most intense in the cauda equina. Bodian stains revealed marked distortion of the axis cylinders. The myelin sheaths were swollen and disrupted. Sections of the femoral nerve revealed an infiltrate consisting predominantly of lymphocytes, although numerous large mononuclear cells with distorted nuclei were present. These inflammatory cells were noted particularly about small vessels. Sections from the facial, acoustic, and phrenic nerves showed slight infiltration. The trigeminal nerves appeared relatively normal.

It is evident, therefore, that the nervous system can be involved in pathologic process as well as any other portion of the body. This involvement appears to be generalized. However, the nature of the nervous system involvement apparently depends on the site most conspicuously implicated.

Incidence: Infectious mononucleosis occurs slightly more frequently in males. There is only one case report of infection in a Negro.[25] This is in accord with the observation of Gorham,[38] who notes that only 12 cases of infectious mononucleosis have been reported as occurring in Negroes. There were 29 males and only six females who had nervous system involvement.

Although infectious mononucleosis is predominantly a disease of children, there is only one report with involvement of the nervous system in a child.[22] The majority of those with nervous system involvement fell into the 20 to 30 age group. The oldest patient was 37 years of age.

It is apparent that the incidence of nervous system involvement is quite small, certainly not over 1 per cent and probably less. The 34 patients with nervous system involvement reported in this review must represent only a small proportion of the total number of cases which occurred between 1931 and 1947. Milne,[39] in reporting a series of 141 cases of infectious mononucleosis occurring over a 10 year period, describes none with involvement of the nervous system. Collins-Williams and Ferguson,[40] in reporting 67 sporadic cases in over a three and a half year period, report that 12 per cent had a "stiff neck." It has become apparent that cervical adenopathy, particularly where the lymph nodes are tender (as they are in infectious mononucleosis), will give rise to nuchal rigidity. It is said that in nuchal rigidity, movement of the neck is limited in the anterior-posterior direction, but that in cases of cervical lymphadenopathy movement is limited in all directions. This point bears further investigation.

In addition to sporadic occurrences, infectious mononucleosis is known to occur in epidemics. Halcrow et al.[41] in 1943 described an epidemic consisting of 296 cases. Only two patients were described as having nuchal rigidity. In the report of an epidemic by Wechsler [22] involving 556 cases,

nine patients had severe headache with mild nuchal rigidity, of which only three had any definite evidence of nervous system involvement. One other patient had a brachial neuritis. This is an incidence of less than 1 per cent.

Incubation Period: Although symptoms of involvement of the nervous system may develop as the presenting symptom, or appear concomitantly with the onset of systemic manifestations, they occur most commonly from one to three weeks subsequent to the onset of the disease.

The extreme variation in the time of appearance of nervous system involvement following onset of infectious mononucleosis does not support the view that this involvement represents an antibody response. Whatever the etiologic agent, it apparently invades the nervous system at the same time that it does other systems. Also to be considered is the concept that the nervous system involvement may be due to activation of a virus already present, or to secondary invasion by another virus. There is no evidence to substantiate such a view.

Spinal Fluid Changes: Spinal fluid changes consist primarily of an increase in cells and/or protein. The pleocytosis, when present, consists mainly in an increase in lymphocytes. There has never been any morphologic description of these cells with regard to any resemblance to "monocytoid" cells. Pressure is elevated in some instances. Occasionally there are changes in the gold curve. Sugar and chlorides are always within normal limits. There are no reports of positive Wassermann reactions. Studies of smears and bacterial cultures have not been fruitful.

There may be changes in the cerebrospinal fluid without mental, motor, or sensory defects. This was first noted by Schmidt and Nyfeldt [8] who, after encountering a patient with meningitis associated with infectious mononucleosis, routinely did lumbar punctures on three subsequent patients in whom there were no signs of nervous system involvement and found changes in the spinal fluid. Coogan et al.[21] also describe two such patients. Five out of six patients with infectious mononucleosis recently observed at the Bronx Veterans Hospital showed abnormal spinal fluids although there was no evidence of involvement of the nervous system. These spinal fluid changes consisted of an elevation of cells and/or protein.

Attempts to detect heterophil antibodies in the spinal fluid have been made on four occasions [8, 13, 25, 26] without success. In the patient described in this paper, the heterophil antibody was not detected in the spinal fluid.

The inability to detect the heterophil antibody in the spinal fluid may be based on the small amount of globulin present in the fluid, even in the presence of an inflammatory process in the meninges. Unfortunately, spinal fluid from the patient reported in this paper was not available for further study after recovery. At the present time, using a modified method, an investigation of spinal fluid of patients with infectious mononucleosis, whether or not clinical evidence of nervous system involvement is present,

is being carried out. Up to this point, using this modified method, all controls (numbering over 300) have been negative, but six patients with infectious mononucleosis, without evidence of nervous system involvement, have shown the presence of heterophil antibodies. In all instances, the substance giving the reaction was absorbed with beef heart but not with guinea pig kidney. This work forms the basis of a separate report.*

Differential Diagnosis: Tidy [42] in 1946 presented the problem of differential diagnosis between meningitis with infectious mononucleosis and benign lymphocytic meningitis. He pointed out that the differential diagnosis depended on "specific and repeated examinations." The detection of the heterophil antibody in the blood should implicate or rule out infectious mononucleosis.

Mumps and infectious mononucleosis may be compared as to nervous system involvement. The etiologic agent of mumps is known to be a virus. Here, too, although the disease occurs equally in both sexes, "neurological complications" are said to occur three times more frequently in males. The symptoms of involvement of the nervous system may introduce the disorder, occur simultaneously with the systemic manifestations, or follow at various intervals after the onset of the disease. The incidence has been estimated at from 1 per cent to 25 per cent. Meningitis, meningo-encephalitis, myelitis, neuronitis, and peripheral neuropathy may occur. A patient with serratus magnus palsy, patients with facial paralysis, and patients with optic neuritis have been described. In many patients, cerebrospinal fluid changes without mental, motor or sensory defects have occurred.[43] De Lavergne [44] and Lightwood [45] have described nervous system involvement in mumps.

Prognosis: Recovery was complete in 85 per cent of patients in periods ranging from a few days to several months. Despite complete symptomatic recovery, many patients showed spinal fluid changes for longer periods of time. In one of Gsell's [5] patients, clinical signs of meningitis were gone by the fifth day, although spinal fluid changes persisted for 81 days. In the patient described by Thelander and Shaw,[12] the spinal fluid showed a pleocytosis four months after onset of the illness. The patients described by Zohman and Silverman,[15] Saksena,[19] and Slade [25] showed residual muscular weakness and wasting. The patient reported by Schneider and Michaelson [26] retained a mild motor aphasia and had difficulty in concentrating. All of these residuals were apparently permanent.

Summary

Since 1931 there have been many reports describing involvement of the nervous system in infectious mononucleosis. A review of the literature up to the time of publication of this paper revealed 28 reports, including 46

* Silberstein, J. K., Bernstein, T. C., and Stern, T.: Demonstration of heterophile antibodies in the cerebrospinal fluid from patients with infectious mononucleosis, J. Lab. and Clin. Med. 33: 1204, 1948.

patients. Of these patients, 34 satisfied criteria for involvement of the nervous system in this disease. Nervous system involvement appears to occur in less than 1 per cent of patients with infectious mononucleosis.

Evidence is presented that many parts of the nervous system may be involved in this disorder, the symptomatology depending on the site of maximal involvement. Serous meningitis, meningitis, encephalitis, meningoencephalitis, polyneuronitis, and peripheral neuropathy have been described. It appears that the nervous system is directly invaded by the unknown agent causing infectious mononucleosis.

Clinical evidence of involvement of the nervous system occurs most commonly in males. The changes in the spinal fluid consist of an increase in lymphocytes and/or protein. Changes in the cerebrospinal fluid as evidence of invasion of the nervous system without any sensory, motor, or mental defects have been described, and there is suggestive evidence that this is a common occurrence.

The prognosis in the series of cases described is excellent, 85 per cent of the patients showing complete recovery.

Since the clinical picture produced by involvement of the nervous system is indistinguishable from that caused by many other agents, heterophil antibody tests should be done on all patients with "idiopathic" diseases of the nervous system. This is particularly important since the systemic signs of infectious mononucleosis may be minimal.

BIBLIOGRAPHY

1. Johansen, A. J.: Serous meningitis and infectious mononucleosis, Acta med. Scandinav. **76**: 269, 1931.
2. Epstein, S. H., and Dameshek, W.: Involvement of the central nervous system in a case of glandular fever, New England J. Med. **205**: 1238, 1931.
3. Fledelius, M.: Augenmusskelamung als Komplikation der Mononucleosis infectiosa, Acta ophth. **13**: 150, 1935.
4. Sucher, A., and Schwarz, E.: Lymphatische Reaktion und Encephalomeningitis, Wien. klin. Wchnschr. **49**: 1417, 1936.
5. Gsell, O.: Meningitis serosa bei Pfeifferschem Drusenfieber (Mononucleosis infectiosa), Deutsche med. Wchnschr. **63**: 1759, 1937.
6. Davidsohn, I.: Serologic diagnosis of infectious mononucleosis, J. A. M. A. **108**: 289, 1937.
7. Huber, E. A.: Serous Meningitis in Pfeifferschem Drusenfieber, Schweiz. med. Wchnschr. **68**: 882, 1938.
8. Schmidt, V., and Nyfeldt, A.: Regarding infectious mononucleosis and meningoencephalitis, Acta oto-laryng. **26**: 680, 1938.
9. Pietzonka, H.: Meningitis serosa bei Pfeifferschem Drusenfieber, Deutsch. Arch. f. klin. Med. **185**: 153, 1939.
10. Thomson, S., and Vimtrup, B.: Six fatal cases of infectious mononucleosis complicated by central respiratory paralysis, Nord. med. **4**: 3295, 1939.
11. Marshall, E. A.: Infectious mononucleosis, Am. J. Clin. Path. **9**: 298, 1939.
12. Thelander, H. E., and Shaw, E. B.: Infectious mononucleosis with special reference to cerebral complications, Am. J. Dis. Child. **61**: 1131, 1941.

13. Landes, R., Reich, J. P., and Perlow, S.: Central nervous system manifestations of infectious mononucleosis, J. A. M. A. **116**: 2482, 1941.
14. Leavell, B. S., and McNeel, J. O.: Infectious mononucleosis: unusual manifestations, Virginia M. Monthly **69**: 180, 1942.
15. Zohman, B. L., and Silverman, E. G.: Infectious mononucleosis and encephalomyelitis, Ann. Int. Med. **16**: 1233, 1942.
16. Richardson, J. S.: Serratus magnus palsy, Lancet **1**: 618, 1942.
17. Hiller R. L, and Fox, M. J.: Infectious neuronitis associated with infectious mononucleosis, Marquette M. Rev. **7**: 152, 1943.
18. Shafer, J., and Weir, J. R.: Meningeal reaction in a case of glandular fever, Brit. M. J. **1**: 218, 1943.
19. Saksena, H. C.: Paralysis of the serratus anterior following glandular fever, Brit. M. J. **2**: 267, 1943.
20. Solomons, B.: Infectious mononucleosis: meningeal features, J. Roy. Nav. M. Serv. **31**: 178, 1945.
21. Coogan, T. S., Martinson, D. L., and Mathews, W. H.: Infectious mononucleosis: neurological symptoms, Illinois M. J. **87**: 296, 1945.
22. Wechsler, H. F., Rosenblum, A. H., and Sills, C. T.: Infectious mononucleosis: report of an epidemic in an army post, Ann. Int. Med. **25**: 256, 1946.
23. Geliebter, S.: Acute infectious mononucleosis complicated by encephalomyelitis, Lancet **2**: 753, 1946.
24. Vaughn, S. L., Regan, J. S., and Terplan, K.: Infectious mononucleosis complicated by spontaneous rupture of the spleen and central nervous system involvement, Blood **1**: 335, 1946.
25. Slade, J.: Involvement of the central nervous system in infectious mononucleosis, New England J. Med. **234**: 753, 1946.
26. Schneider, T., and Michaelson, D. A.: Central system manifestations of glandular fever, South African M. J. **21**: 57, 1947.
27. Ricker, W., Blumberg, A., Peters, C. H., and Widerman, A.: The association of the Guillain-Barré syndrome with infectious mononucleosis, Blood **2**: 217, 1947.
28. Ashworth, J., and Motto, S.: Infectious mononucleosis complicated by bilateral papilloretinal edema, New England J. Med. **237**: 544, 1947.
29. Murray, E. G. D., Webb, R. A., and Swann, M. B. R.: Disease of rabbits characterized by large mononuclear leukocytes, J. Path. and Bact. **29**: 407, 1926.
30. Nyfeldt, A.: Etiologie de la mononucleose infectieuse, Compt. rend. Soc. de biol. **33**: 218, 1935.
31. Bland, J. O. W.: Glandular fever: experimental investigation, Lancet **2**: 521, 1930.
32. Van den Bergh, L., and Liessens, P.: Transmission de la mononucleose infectieuse humanine au Macacus rhesus, Compt. rend. Soc. de biol. **132**: 90, 1939.
33. Julianelle, L. A., Bierbaum, O. S., and Moore, C. V.: Studies on infectious mononucleosis, Ann. Int. Med. **20**: 281, 1944.
34. Burnet, F. M., and Anderson, S. G.: Modification of human red cells by virus action. II. Agglutination of modified human red cells by sera from cases of infectious mononucleosis, Brit. J. Exper. Path. **27**: 236, 1946.
35. Downey, H., and Stasney, J.: The pathology of lymph nodes in infectious mononucleosis, Folia haemat. **54**: 417, 1935–6.
36. Gall, E. A., and Stout, H. A.: Histological lesions in lymph nodes in infectious mononucleosis, Am. J. Path. **16**: 443, 1940.
37. Allen, F. H., and Kellner, A.: Infectious mononucleosis, Am. J. Path. **23**: 463, 1947.
38. Gorham, L. W.: Infectious mononucleosis (from Cecil's Textbook of medicine), 1947, W. B. Saunders and Company, Philadelphia, p. 515.
39. Milne, J.: Infectious mononucleosis, New England J. Med. **233**: 727, 1945.

40. Collins-Williams, C. T., and Ferguson, C. C.: Infectious mononucleosis, Canad. M. A. J. **55**: 17, 1946.
41. Halcrow, J. P. A., Owen, L. M., and Roger, N. O.: Infectious mononucleosis: report of an epidemic, Brit. M. J. **2**: 443, 1943.
42. Tidy, H. L.: Relationship of benign lymphocytic meningitis and glandular fever, Lancet **2**: 819, 1946.
43. Wesselhoeft, C.: Medical progress (mumps), New England J. Med. **226**: 530, 1942.
44. de Lavergne, V., Kissel, P., and Accoyer, H.: Étude sur la periode d'incubation des "oreillons," Bull. Acad. de méd., Paris **119**: 534, 1938.
45. Lightwood: Myelitis from mumps, Brit. M. J. **1**: 484, 1946.
46. Bonnin, H., and Bergouignan, A.: Infectious mononucleosis with curable meningoencephalitis and temporary coma, Bull. et mém. Soc. méd. d. hôp. de Paris **64**: 39, 1948.
47. Field, W. W.: Severe central nervous system involvement in infectious mononucleosis, Am. J. Med. **4**: 154, 1948.
48. Payn, S. B.: Virus meningitis and infectious mononucleosis, N. Y. State J. Med. **48**: 631, 1948.
49. Raymond, R. W., and Williams, R. L.: Infectious mononucleosis with psychosis, N. Eng. J. Med. **239**: 542, 1948.
50. de Vita, P.: Meningoradiculitis due to infectious mononucleosis, Gior. di clin. med. **29**: 593, 1948.
51. Bickel, G., Mach, R., della Santa, R., and Ducommun, P.: Neurologic forms of mononucleosis, Schweiz. med. Wchnschr. **78**: 938, 1948.
52. Karpe, G., and Wising, P.: Infectious mononucleosis. Retinal changes with acute reduction of vision as the initial symptom, Acta ophth. **26**: 19, 1948.
53. Bercel, N. A.: The electro-encephalogram in cerebral complications of infectious mononucleosis, J. Nerv. and Ment. Dis. **107**: 537, 1948.
54. Dolgopol, V. B., and Husson, G. S.: Infectious mononucleosis with neurologic complications, Arch. Int. Med. **83**: 179, 1949.
55. Bickel, G.: Les formes nerveuses et ménengées de l'angine à monocytes et de la mononucleose infectieuse, Pract. otorhinolar. **11**: 79, 1949.
56. Graham, S. D., Schwartz, W. H., and Chapman, W. L.: Infectious neuronitis complicating infectious mononucleosis, U. S. Nav. Med. Bull. **49**: 914, 1949.
57. Haymaker, Webb, and Kernohan, J. W.: The Landry-Guillain-Barré syndrome, Medicine **28**: 59, 1949.

CATION EXCHANGE RESINS IN THE TREATMENT OF CONGESTIVE HEART FAILURE *

By SAMUEL H. HAY, M.D., and J. EDWIN WOOD, JR., M.D., F.A.C.P.,
Charlottesville, Virginia

ADEQUATE control of sodium dietary intake has always been a vexing problem. The vagaries of the average patient tend to vitiate attempts at suitable sodium restriction in patients with edema or potential congestion. Appetizing and nutritious salt-free diets are difficult to arrange. The prevention of sodium absorption from ingested food would seem worthy of trial. Such a possibility lies in the use of a cation exchange resin which on oral ingestion mixes with the food, fixes certain basic electrolytes, and carries them out in the feces. It is the purpose of this study to describe our clinical experiences with such a substance and certain effects on urinary sodium and potassium excretion following its administration.

A total of 10 patients with and without edema have been studied for long and short periods. It appears that gastrointestinal sodium absorption may be effectively blocked, diuresis initiated at times, and mercurial diuresis potentiated considerably by the use of this agent. These and additional events associated with the administration of several cation exchange resins will be amplified and described below.

In 1934 Adams and Holmes produced the first synthetic ion exchange resins, although similar materials had been used in such processes as sugar refining as far back as 1896. At present ion exchangers are used in many commercial processes, from the softening of water to the preparation of pharmaceuticals, because of their ability to isolate specific anions and cations.

The clinical use of anion exchange resins was first suggested in 1945 for the reduction of gastric acidity in the treatment of peptic ulcer.[1, 2, 3, 4, 5, 6, 7] In 1946 Dock [8] pointed out the nontoxicity of an orally administered cation exchange resin (Ionca C 200 and C 284) in rats and dogs and demonstrated its effectiveness in increasing the fecal excretion of sodium. Berger et al.[9] have published a careful balance study of the effect on the urinary and fecal excretions and on the serum levels of sodium, potassium and calcium produced by prolonged administration of a sulfonated cation exchange resin. In addition, they presented the preliminary evidence of its possible effectiveness in the control of heart failure and of the ascites associated with cirrhosis. Heming and Nance [10] have carried out extensive studies in rats and dogs on an ammonium cation resin which has been used in the cases reported here,

* Received for publication June 23, 1950.
From the Cardiovascular Division of Internal Medicine, Department of Medicine, University of Virginia Medical School, Charlottesville, Virginia.
Aided by a grant from the U. S. Public Health Service (Research Grant H-124) and by Sally Twyman Research Fund.

and they have found no evidence of toxicity. Rats maintained on a diet 10 per cent of which by weight was this resin have shown no signs of hematologic or other toxic effects through two generations. Balance study of iron, copper, magnesium, and manganese revealed no appreciable fecal loss of any of these elements. Preliminary evidence from the work of Nance in humans suggests that this resin does not interfere with vitamin absorption.

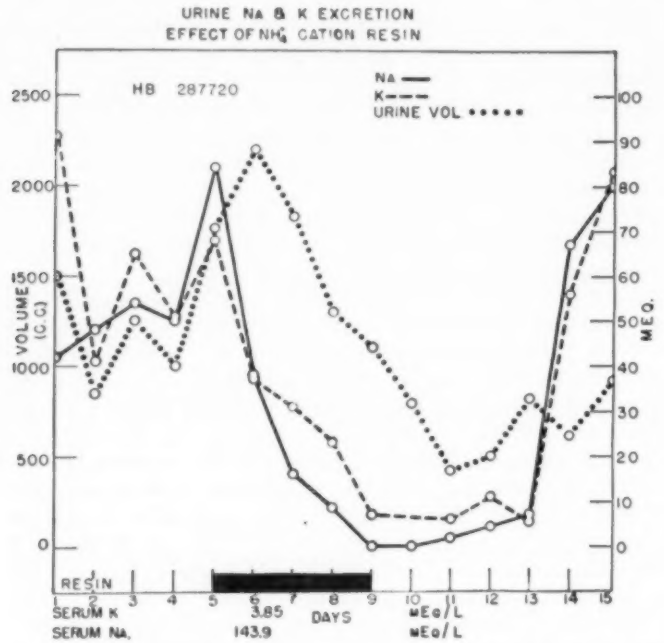


FIG. 1. H. B., a patient with rheumatoid arthritis but without edema or circulatory disease who received 45 grams daily of ammonium cation resin for four days. Note fall in Na and K excretion in urine. Patient on regular diet at the time.

Clinical studies of the effect of ammonium and potassium carboxylate cation exchange resins * on the sodium and potassium serum levels and on the urinary excretion of sodium and potassium were carried out on several relatively normal persons and on certain patients. No attempt at balance study was made, and patients were observed both in and out of the hospital under usual conditions of treatment. All patients were on a diet containing

* The resins (648 and 741Y) used in this study were kindly supplied by Smith, Kline and French of Philadelphia, Pennsylvania. These are preparations of a carboxylated resin (amberlite 96); the average dosage was 45 gm. a day, given with meals in divided doses. This was originally supplied in the form of a micropulverized powder; later preparations had the pulvules bound in acacia granules.

approximately 1,000 mg. of sodium, unless otherwise stated. It is obvious from urinary excretion of sodium that they did not follow this diet except during hospitalization. Serum sodium was done by the Butler-Tuthill [11] gravimetric method, and urinary sodium and potassium and serum potassium were done with an Internal Standard Flame Photometer.[12]

Altogether, 10 patients have been studied from three to 180 days. Of these, three had congestive heart failure, two no evidence of congestion or edema, three cirrhosis of the liver, one constrictive pericarditis, and one chronic glomerulonephritis.

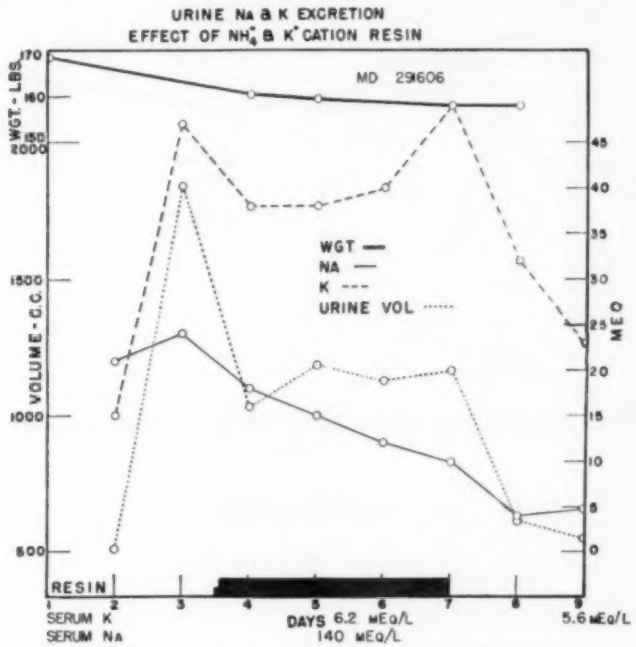


FIG. 2. M. D., a patient with hypertensive cardiovascular disease but without edema receiving 45 grams daily of ammonium-potassium resin (two mEq of K per gram resin). Note sustained serum potassium level and continued potassium excretion in urine.

Figures 1 and 2 illustrate the effects of resin administration on the urinary excretion of sodium and potassium, as well as on the serum levels in normal controls. The patient whose studies are shown in figure 1 was on a regular diet, but the urinary sodium and potassium excretions were markedly reduced accompanying the ingestion of 45 gm. a day of ammonium cation resin. The patient of figure 2 was on a 1,000 mg. sodium diet; 45 gm. of ammonium-potassium (90 mEq. of potassium) resin a day were

effective in reducing the sodium excretion while the serum level and the urinary excretion of potassium were maintained.

Three patients with heart failure were given resin. The first patient received resin for four days and had a significant diuresis which had, however, begun prior to resin on bed rest alone. Excretion and weight curves on the second patient are shown in figure 3:

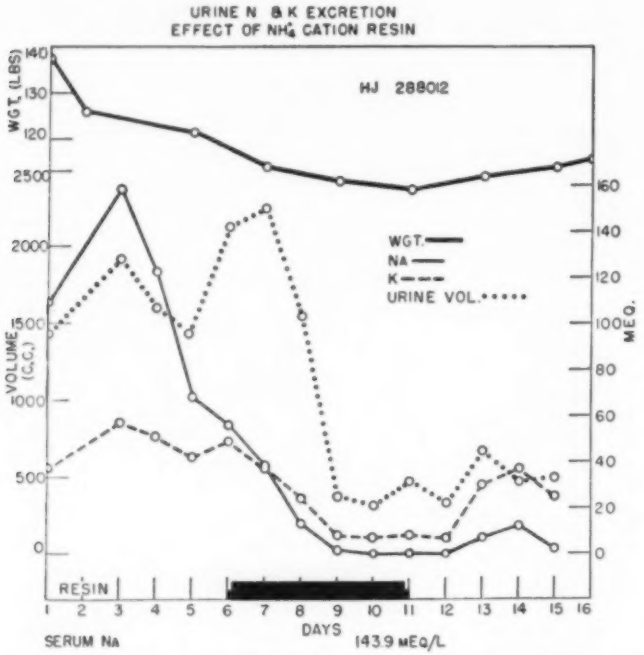


FIG. 3. H. J., effect of ammonium cation resin on patient with arteriosclerotic heart disease and congestive heart failure. Patient was receiving 1,000 mg. low sodium diet.

Patient H. J. was a 63 year old man with known congestive failure treated with digitoxin and a low sodium diet for at least six months. Upon his admission to the hospital it was felt that he had arteriosclerotic heart disease and congestive failure, as evidenced by hepatic enlargement and peripheral edema. He was managed with bed rest and digitoxin, and was given ammonium cation resin, 15 gm. three times a day for seven days. His weight fell from 137.5 pounds to 109 pounds during therapy; a gain of six and one-half pounds occurred subsequent to the discontinuation of the resin. After three days on the resin the patient became dizzy, weak, and lightheaded, and showed numerous ventricular premature beats with resulting bigeminy. Following cessation of digitoxin, these symptoms and signs cleared.

The part played by bed rest in the diuresis in this case is undeniable; however, the tendency to gain weight after discontinuation of the resin is

certainly established. It was felt that lowering of the serum potassium level may have in some way influenced the appearance of digitalis intoxication, although the diuresis may have produced this effect. This case illustrates the short-term use of the resin in the management of congestive heart failure.

Long-term utilization of the resin in congestive heart failure on an out-patient basis is possible (figure 4):

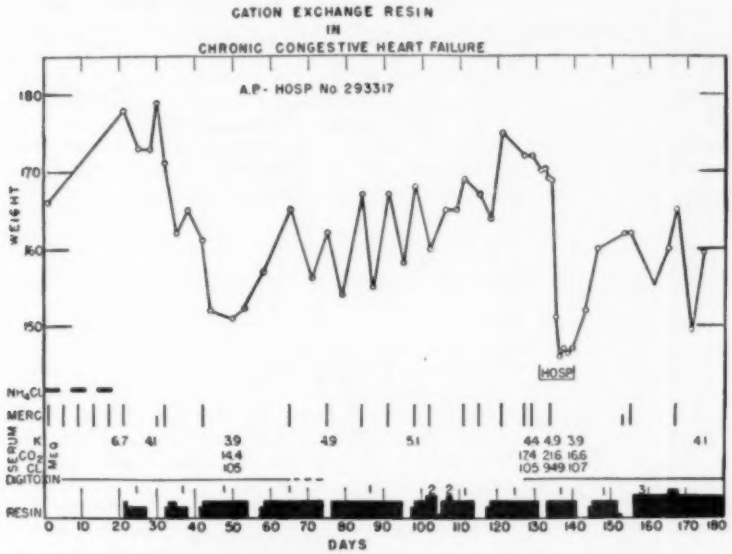


FIG. 4. A. P., a patient with hypertensive heart disease and chronic congestive heart failure. Single vertical lines represent 2 c.c. mercury diuretic. Ammonium chloride not used after beginning of resin administration. Digitalization maintained with digitoxin except as noted by interruption of horizontal line. Resin administered in dosage of 30 to 60 grams, 1 ammonium cation resin, 2 ammonium potassium cation resin (2 mEq K per gram resin) and 3 ammonium-potassium cation resin (1 1/3 mEq K per gram resin).

Patient A. P. was a 43 year old man who developed progressive heart failure with sustained hypertension in spite of bilateral lumbar sympathectomy. Congestive failure was continually manifested by dyspnea and orthopnea, in addition to marked basal râles, cardiomegaly, hepatomegaly, and marked ankle edema. Digitoxin, low sodium diet, and ammonium chloride were utilized, but mercurial diuresis was still necessary every three to four days. He was begun on ammonium cation resin, with marked weight loss and diminution in frequency of mercurial injections until the patient spontaneously discontinued digitoxin. Return of massive edema ensued, but he was redigitalized and hospitalized, with improvement, after which maintenance has been moderately successful on an out-patient basis.

This case illustrates the fact that resin is more effective than ammonium chloride alone in increasing the effect of mercurial diuresis in chronic congestive failure. In addition, it is apparent that relative long-term use of the

material is possible without the appearance of toxic effects. Diet and digitalis were not well controlled in this patient, making his control without resin virtually impossible. Since maintenance on resin was begun, he has been able to carry on his occupation as a clerk.

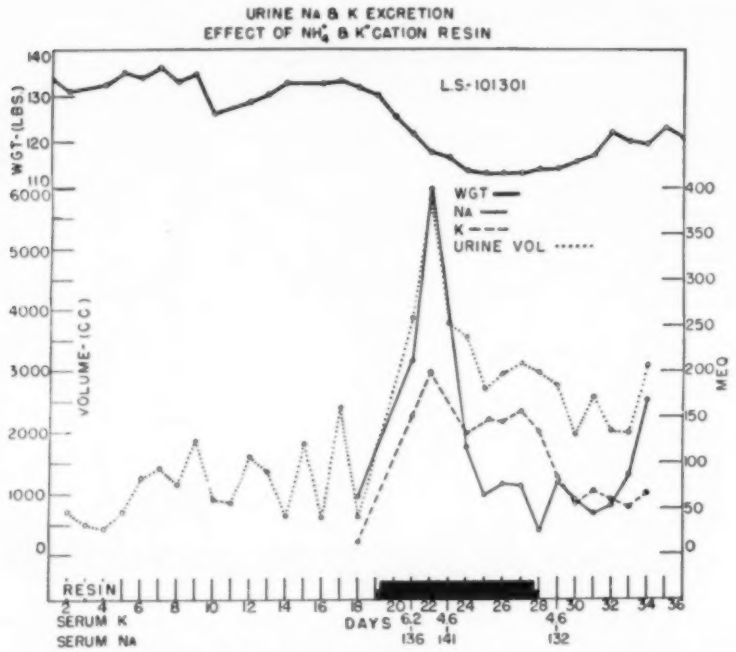


FIG. 5. L. S., a patient with cirrhosis of the liver and marked ascites. Diuresis with administration of resin.

Three cases of Laennec's cirrhosis with ascites and edema have been studied; favorable results were obtained in two of the three with resin. Figure 5 is graphic evidence of the marked diuresis which occurred in one patient.

Patient L. S. was a 44 year old woman who was admitted to the hospital because of ascites and edema subsequent to a prolonged period in which poor nutrition was associated with a considerable consumption of alcohol. Diagnosis of Laennec's cirrhosis was made on the basis of clinical findings and liver biopsy. She was placed on a high protein-high caloric diet, with vitamin supplements and choline as well as intraheptol. In spite of this therapy repeated paracentesis was necessary. Fifteen grams three times a day of ammonium-potassium cation resin (two mEq. of potassium per gram) were begun and continued for nine days, during which time a remarkable diuresis with loss of edema and ascites occurred. Reaccumulation of edema and

ascites began following cessation of the resin, but the patient left the hospital. The two distinct losses of weight shown prior to resin were the result of fluid loss from paracentesis. Serum chloride was 105.2 mEq. per liter and CO_2 combining power 20 to 23 mEq. per liter during resin therapy.

This diuresis may have been spontaneous and unrelated to the resin; however, the immediate return of ascites following cessation of resin is striking. In contrast, another similar patient was unresponsive.

Patient B. W. was a 52 year old woman admitted for progressive swelling of the abdomen and ankles and for increasing orthopnea and dyspnea. On the day of admission she vomited a small amount of bright red blood and had a tarry stool. A history of marked alcoholism was obtained. Examination revealed an icteric woman with numerous spider nevi, ascites, ankle edema, and hepatomegaly. Liver biopsy showed nodular cirrhosis, and this diagnosis was confirmed at autopsy when the patient died from massive hematemesis from esophageal varices. Forty-five grams of resin were given for four days during the hospitalization period without considerable effect.

A fair trial of resin was not obtained in this patient; prolongation of therapy might have produced a diuresis but would not have prevented hemorrhage.

Patient J. C. was a 52 year old coal miner who entered the hospital because of progressive swelling of his abdomen, legs, and scrotum for two months in spite of four paracenteses on the outside. History revealed a considerable intake of alcohol over a 12 year period associated with a poor diet. Examination disclosed a moderately well developed middle-aged man who had marked ascites, 4 plus peripheral and scrotal edema, and 2 plus sacral edema. Several spider angiomata were noted on the chest and neck. Considerable hepatomegaly was found after paracentesis. A diagnosis of hepatic cirrhosis was confirmed by liver biopsy. In spite of therapy with a high protein-high carbohydrate diet, intraheptol, choline, vitamins, and mercurial diuresis, repeated paracentesis was necessary. He was placed on 45 to 60 gm. of ammonium-potassium resin a day and was able to maintain his weight without further therapy. Mercurials produced a 13 pound diuresis where previously they had been ineffective. Resin was stopped preparatory to a splenorenal-shunt operation, and the patient gained 15 pounds in three days in spite of mercurial diuresis.

This is another example of the salutary effect of resin on a mercurial diuresis. Two of these three cases seem to have shown a favorable response to the use of resin in cirrhosis.

Two other patients were tried on the cation exchange resin. The first showed a fair response as indicated by reduction in the ascites resulting from constrictive pericarditis. The second, in the nephrotic stage of chronic glomerulonephritis, showed no remarkable improvement.

Patient D. W., a 29 year old colored male, was first admitted to the medical service with an acute pericardial effusion from which no organism was isolated. There was a gradual appearance of ascites and peripheral edema over a several month period. In spite of operative removal of a segment of thickened pericardium, hepatomegaly, ascites, and edema persisted. Two months postoperatively a 1,000 mg. sodium diet, in addition to intermittent ammonium chloride and mercurial diuresis, was still in-

adequate in control of ascites. He was begun on a resin and went from 156 to 149 pounds before he stopped taking this material regularly and ascites returned. His weight then reached 164 pounds, after which resin and Thiomerin returned him to 152 pounds. In one week off the resin he regained eight pounds.

Patient W. B. was a 40 year old colored male with a one month's history of progressive edema and ascites and a gain of nearly 100 pounds. No history of acute nephritis could be obtained. Examination revealed marked ascites and ankle edema, in addition to a blood pressure of 150/100 mm. Hg and small fundal exudates and one retinal hemorrhage. The urine contained 5 to 15 gm. of albumin per 24 hours and a few granular casts; specific gravity varied between 1.005 and 1.012. The patient was felt to be in the nephrotic stage of glomerulonephritis and was treated with a low sodium diet and mercurial diuretics, to which there was a limited response. Cation exchange resin was administered for 10 days, during which time the patient lost only two pounds of weight; dosage was 45 to 60 gm. a day. Subsequently, a moderate diuresis was obtained with concentrated serum albumin.

Discussion

This resin is a phenol-formaldehyde polymer [13] of huge molecular weight which is produced from turpentines. It exists as a sort of homogeneous gel, over the surface of which are arranged many carboxylic acid radicals serving as the sole ion active groups. This enables the cations bound to be remote from the skeleton of the molecule and thus available for exchange.[14] The size of the molecule gives it adsorptive properties also. The affinity of the resin for various cations is a function of molecular size and magnitude of charge as well as of concentration.[15] Since there is little disparity between the molecular weights of sodium and potassium, the differential uptake is largely a matter of the relative concentrations of the two molecules.

The exchange power of the resin becomes activated at a pH of about 6, reaching its maximum operating efficiency at a pH of 8; the reaction may be diagrammatically represented as follows:

$$NH_4R + HCl \underset{\longleftarrow}{\overset{pH<6}{\longrightarrow}} NH_4Cl + HR$$

$$HR + NaCl \underset{\longleftarrow}{\overset{pH>6}{\longrightarrow}} NaR + HCl$$

The ammonium chloride is absorbed while the sodium, bound to the resin, continues down the gastrointestinal tract. Since the binding capacity of this resin is approximately four and one-half to five mEq. per gram, the usual dosage supplies approximately 10 to 12 gm. of ammonium chloride a day. Fecal sodium and potassium levels are greatly augmented as urinary excretion of the cations falls to an insignificant level. The serum chloride tends to become elevated and urinary ammonium is greatly increased as administration continues.[9] Serum sodium and potassium levels tend to decline; no serious sodium depletion has been produced in our study, but hypokalemia has resulted. As illustrated in Case H. J., probable hypokalemia was associated with signs of digitalis intoxication. This has been

noted by other workers also. Several investigators have previously commented on the relationship of potassium to cardiac irritability and its possible antagonistic effect to ventricular irritability produced by digitalis.[16, 17, 18] The appearance of ventricular extrasystoles associated with hypokalemia alone has been noted.[19] Toxic amounts of digitalis actually displace potassium from cardiac muscle under experimental conditions; this displaced potassium may be replaced by raising the serum potassium level.[20]

In an effort to surmount the problem of hypokalemia, various amounts of a potassium salt of the resin have been mixed with the ammonium form. It is felt that potassium chloride is produced in the stomach and that appreciable amounts of this salt are absorbed in the upper intestine before the proper pH for activation of the resin is attained.[10] In this manner hypokalemia may be avoided, although hyperkalemia may become a problem where renal function is reduced. Use of this type of resin, with proper control of serum potassium levels, offers a simple remedy for what appeared to be a formidable danger.

Probably because of the low concentration of calcium in the gastrointestinal tract,[9] serious depletion of this cation has not been encountered. Eighteen milliequivalents of calcium a day administered between feedings is considered sufficient in amount to allow adequate absorption.[10]

Fecal nitrogen excretion has not been increased by this material, but careful evaluation of its effect on the absorption of basic organic materials needs investigation if long term resin administration is to be practiced.

Two practical problems have arisen concerning the use of this resin—its impalatability and its tendency to produce gritty, constipating stools. The former, a result of its insolubility, may be circumvented by mixing with certain foods or by suspension in relatively heavy liquids such as tomato juice. The latter arises only with prolonged and constant administration which we have found generally unsatisfactory.

Cation resin therapy in our experience has been most promising in the control of edema due to congestive failure and that due to hepatic cirrhosis; it has been less helpful in the management of the nephrotic state. We have not tried this material on patients with edema associated with toxemias of pregnancy. Moderate success was obtained in reducing the distress of ascites resulting from constrictive pericarditis.

No further comment need be made as to the mechanism of this substance as a means of reducing sodium intake. As a diuretic agent the resin is most effectively used in intermittent fashion; this would be expected, since renal ammonia formation becomes maximal after four to five days. As an adjunct to mercurial diuresis, this intermittent dosage schedule seems worthy of additional study. Two of the cases above, one with heart failure and one with cirrhosis, seem to illustrate the fact that the resin is more effective than ammonium chloride alone in potentiating the effects of mercurial diuresis. Whether the effect of sodium restriction alone may have diuretic powers, as

suggested by Peters,[21] is not clear. With much larger doses of resin it may be possible to remove a considerable amount of the body's extracellular sodium, as has been accomplished already in the case of potassium. Perhaps insufficient dosage accounts for the failures described above.

The use of plain ammonium resin to reduce hyperkalemia in renal insufficiency presents another problem. Development of acidosis would most likely be the greatest limiting factor besides the frequent association of vomiting with this state.

Since many patients on low salt diets continue wilfully or unknowingly to take in much more than their allotted quantities of sodium, exploration of the use of resin in the treatment of hypertension and heart failure on a long term basis should be undertaken.

Summary and Conclusion

1. Ten individuals with and without edema have been studied following the administration of a cation resin.

2. Administration of an ammonium cation resin reduces both sodium and potassium excretion in the urine.

3. The consequent reduction of sodium absorption from the intestine is effective in the management of congestive heart failure and in certain instances of cirrhosis of the liver with ascites.

4. Hypokalemia originally encountered following the ammonium cation resin does not occur with the ammonium-potassium cation resin.

5. The resultant ammonium chloride absorption following administration of these resins and the interference with base absorption lead to a mild to moderate acidosis. Effective plasma chloride levels are maintained and mercurial diuresis potentiated.

6. This ammonium chloride effect suggests care in administration of the resins to patients with renal insufficiency and bespeaks intermittent use of the resin in all cases.

7. We have encountered no unfavorable symptoms or signs following the use of the ammonium-potassium cation resin. The low salt syndrome has not occurred in this study.

Following the ammonium cation resin, increased digitalis toxicity may have occurred as a result of hypokalemia in one case.

BIBLIOGRAPHY

1. Segal, H. L., Hodge, H., Watson, J. S., and Scott, W. J. M.: A polyamine-formaldehyde resin. I. Its effect upon the pH of acidified solutions and the pH and pepsin of gastric juices in vitro. II. Its toxicity in rats: preliminary feeding tests, Gastroenterology **4**: 484–496, 1945.

2. Martin, G. J., and Wilkinson, J.: The neutralization of gastric acidity with anion exchange resin, Gastroenterology **6**: 315–323, 1946.

3. Spears, M. N., and Pfeiffer, C. J.: Anion exchange resin and peptic ulcer pain, Gastroenterology **8**: 191–198, 1947.
4. Segal, H. L., Hodge, H., Watson, J. S., and Scott, W. J. M.: III. Chronic toxicity experiments in rats, Gastroenterology **8**: 199–201, 1947.
5. Fraemer, M., and Lehman, D. J.: The treatment of peptic ulcer with anion exchange resins, Gastroenterology **8**: 202–204, 1947.
6. Marks, J. A.: An anion exchange resin for the medical management of peptic ulcer, Rev. Gastroenterol. **16**: 82–84, 1949.
7. Wirts, C. W., and Rehfuss, M. E.: A study of the effect of an anion exchange resin on gastric and duodenal secretions and gastric emptying, J. Clin. Investigation **19**: 37–45, 1950.
8. Dock, W.: Sodium depletion as a therapeutic procedure: the value of ion exchange resins in withdrawing sodium from the body, Tr. A. Am. Physicians **59**: 282–285, 1946.
9. Erwin, L., Berger, E. V., Rosenburg, V., and Jockenthal, R.: Effect of cation exchange resin on electrolyte balance and its use in edematous states, J. Clin. Investigation **28**: 1403–1411, 1949.
10. Heming, A. E., and Nance, J.: Unpublished data, personal communication.
11. Butler, A. M., and Tuthill, E.: An application of the uranyl zinc acetate method for determination of sodium in biological material, J. Biol. Chem. **93**: 171–180, 1931.
12. Berry, J. W., Chappell, D. G., and Barnes, R. B.: Improved method of flame photometry, Indust. and Engin. Chem. (Analytical Edition) **18**: 19–24, 1946.
13. Tompkins, E. R., Khym, J. X., and Cohn, W. E.: Ion exchange as a separations method, J. Am. Chem. Soc. **69**: 2769–2777, 1947.
14. Bauman, W. C., and Eichhorn, J.: Fundamental properties of a synthetic cation exchange resin, J. Am. Chem. Soc. **69**: 2830–2836, 1947.
15. Boyd, G. E., Schubert, J., and Adamson, A. W.: The exchange absorption of ions from aqueous solutions by organic zeolites, J. Am. Chem. Soc. **69**: 2818–2829, 1947.
16. Sampson, J. J., and Anderson, E. M.: The treatment of certain cardiac arrhythmias with potassium salts, J. A. M. A. **99**: 2257–2261, 1932.
17. Stempein, S. J., and Katz, K. H.: Quinidine and potassium in the treatment of refractory paroxysmal ventricular tachycardia, Am. Heart J. **24**: 555–558, 1942.
18. Enseberg, C. D., Simmon, H. G., and Minta, A.: The effects of potassium upon the heart, with special reference to the possibility of treatment of toxic arrhythmias due to digitalis, Am. Heart J. **39**: 713–728, 1950.
19. Bellet, S., Nadler, C. S., Gazes, P. C., and Lanning, M.: The effect of vomiting due to intestinal obstruction on serum potassium, Am. J. Med. **6**: 712–721, 1949.
20. Friedman, M., and Bine, R., Jr.: Observations concerning the influence of potassium upon the action of a digitalis glycoside (lanatoside C), Am. J. M. Sc. **214**: 633–638, 1947.
21. Peters, J. P.: Water balance in health and disease. Diseases of metabolism, Duncan G. C., 2nd ed., 1947, W. B. Saunders Co., Philadelphia.

PATTERNS OF PULMONARY FIBROSIS AS RELATED TO PULMONARY FUNCTION *

By DAVID M. SPAIN, M.D., *Valhalla, New York*

DISCREPANCIES are frequently noted between the degree of lung involvement as shown by the roentgenogram and the severity of subjective symptoms of the patient. With the advent of pulmonary functional studies, such as bronchospirometry and pulmonary artery catheterization, discrepancies were still observed between the degree of functional impairment and the degree of involvement on the roentgen-ray picture. It is also well known that there is often very little correlation between cardiorespiratory insufficiency that is observed in silicotics and the degree of pulmonary involvement as seen both on roentgenographic picture and at postmortem examination. Reisner,[1] in a review of sarcoidosis, stated that among 33 patients with pulmonary involvement "there was no definite correlation between the extent of lung involvement and the severity of subjective symptoms, since even among the patients with marked pulmonary lesions, not infrequently symptoms either absent or of a mild degree, are quite out of proportion with what one would expect on the basis of roentgenological findings."

An analysis of the postmortem examinations on a great variety of pulmonary conditions observed over a period of 10 years at Bellevue Hospital indicates that it is the pattern and distribution of the fibrosis in the lungs rather than the degree of fibrosis that is more closely correlated with the severity of both the objective and subjective clinical manifestations. It is these patterns of fibrosis that will to a great extent determine the degree and type of respiratory, ventilatory, combined respiratory and ventilatory, and cardiopulmonary disturbances. An understanding of the mechanism whereby the different patterns of fibrosis disturb pulmonary function will to a great measure explain what appear to be discrepancies between the degree of both subjective and objective pulmonary disturbances in the patients and what is seen on the roentgenographic picture. An illustration of the important rôle that fibrosis plays in the disturbances of pulmonary function can be seen in cases of siderosis. In siderosis, despite marked changes that are seen on the roentgenogram, the patients do not suffer from any significant degree of pulmonary dysfunction. The answer to this lies in the fact that there is no fibrotic response to the iron particles deposited in the lungs.

Although this report is concerned primarily with patterns of pulmonary fibrosis as related to pulmonary function, it is important to avoid a mechanical approach to this problem. The status of pulmonary function at any given time depends on the dynamic interplay of the anatomic alterations

* Received for publication April 5, 1949.
From the Laboratories of Pathology and the Chest Division (Columbia University) of Bellevue Hospital.

caused by fibrosis, variations in the blood supply (volume and composition), the neuromuscular apparatus, and the chemical stimulation of the brain centers. It should also be noted that in many disease entities several different patterns of fibrosis may co-exist.

The destructive effects of inflammatory and neoplastic processes on the pulmonary parenchyma are well known. Aside from these effects, probably the most significant results of damage to the lungs are due to the sequelae associated with fibrosis. It is this fibrosis of the lungs which results from various forms of injury and disease that very often determines what the future outcome of a case will be.

Fibrosis of the lungs may be distributed in five different patterns, namely, bronchial, interstitial, parenchymal, vascular and pleural. Extensive studies by Baldwin, Cournand and Richards [2] have detailed the functional and clinical changes observed in some of these types of fibrosis. The types of fibrosis observed obviously depend upon the etiologic agents and associated disease processes that produce the fibrosis (see table 1).

TABLE I

A Partial List of Conditions Associated with Various Patterns of Pulmonary Fibrosis *

I. *Bronchiolar Fibrosis:*
- a. Chronic bronchitis
- b. Diffuse bronchiolectasis
- c. Phosgene poisoning, etc.
- d. Boeck's sarcoid
- e. Silicosis (asbestosis, diatomaceous earth, talc, etc.)
- f. Tuberculosis (repeated spreads of bronchogenic dissemination with healing)

II. *Interstitial Fibrosis:*
- a. Acute interstitial fibrosis
- b. Chronic interstitial fibrosis (etiology undetermined)
- c. Beryllium poisoning
- d. Scleroderma
- e. Advanced chronic passive congestion of lung (secondary to mitral stenosis)
- f. Congenital dysplasia of the lung
- g. Bauxite

III. *Parenchymal (Intra-alveolar) Fibrosis:*
- a. Unresolved pneumonia with organization (streptococcus, Friedlander's, tuberculous)
- b. Radiation pneumonia
- c. Silicosis
- d. Lipoid pneumonia

IV. *Vascular Fibrosis:*
- a. Schistosomiasis
- b. Foreign body emboli
- c. Diffuse lymphangitic carcinomatosis with carcinomatous endarteritis
- d. Primary pulmonary arteriolarsclerosis
- e. Periarteritis nodosa of pulmonary vessels
- f. Rheumatic arteritis

V. *Pleural Fibrosis:*
- a. Chronic pyogenic empyema
- b. Tuberculous empyema
- c. Hemothorax

* In certain of these conditions several patterns of fibrosis will co-exist, in particular, tuberculosis and some forms of silicosis.

Fibrosis Related to the Bronchial Tree

The bronchial tree may become involved in all types of inflammation—acute, chronic, suppurative, non-suppurative, etc. If the inflammatory process is induced by such an agent as phosgene, a superficial ulceration of the bronchial mucosa may develop. The ensuing reparative response may fill the bronchial lumen with granulation tissue. This has at times produced a

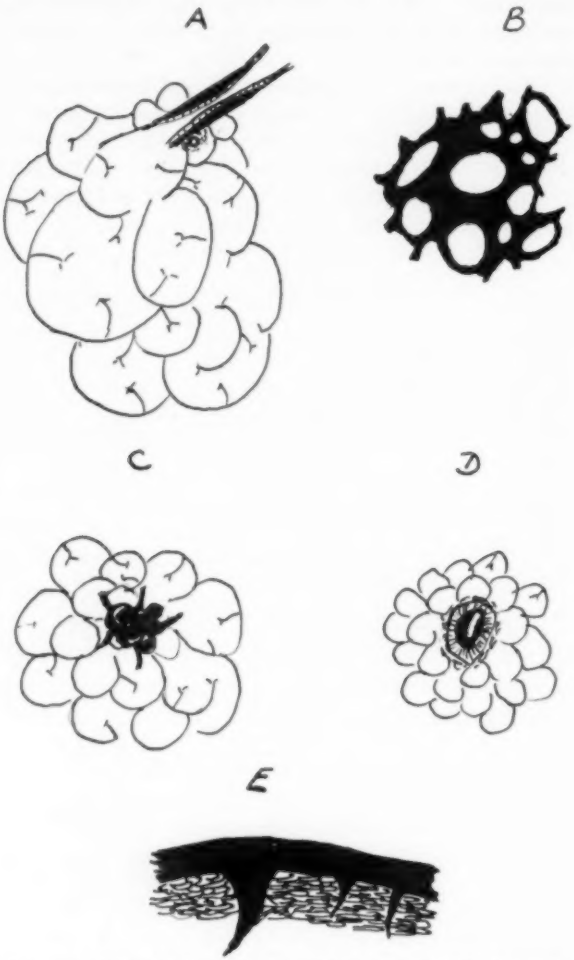


Fig. 1. Schematic illustrations of: A—Bronchiolar fibrosis with obstructive emphysema. B—Interstitial fibrosis. C—Intra-alveolar (parenchymal) fibrosis with surrounding distention emphysema. D—Arteriolarsclerosis. E—Pleural fibrosis with compression of lung.

condition known as "bronchiolitis fibrosis obliterans." If the inflammatory process is suppurative, destruction of the bronchiolar and bronchial walls may take place. This is followed by both dilatation and fibrosis of the bronchioles. On the other hand, if a mild chronic inflammatory process is present, there may be no significant destruction of the bronchiolar wall. The fibrous tissue may be deposited within or around the walls of these bronchioles. This will either narrow the bronchiolar lumen or impart a rigidity to the bronchiolar wall. The main sequela of this type of fibrosis is obstructive emphysema (figure 1). If the chronic bronchiolar inflammatory process is widespread, a diffuse obstructive emphysema will develop. Therefore, the pattern of fibrosis most often related to the development of obstructive emphysema is usually confined to the bronchiolar tree. The parenchyma

TABLE II

Relationship of Pattern of Fibrosis to Pulmonary Dysfunction and Emphysema

Type of Fibrosis	Type of Emphysema Present	Type of Physiologic Dysfunction	Incidence of Pulmonary Hypertension with Cor Pulmonale
1. Bronchiolar fibrosis	Diffuse obstructive	Ventilatory	Most frequent
2. Interstitial fibrosis	None	Respiratory	Frequent
3. Parenchymal (intra-alveolar) fibrosis	Distention emphysema	No significant dysfunction (except in marked involvement)	Does not occur
4. Vascular fibrosis	Nutritional emphysema	Increase of resistance to flow of blood through lungs. Diffuse disturbance	Frequent
5. Pleural fibrosis	Compression atelectasis of involved side. Distention emphysema of contralateral side	Ventilatory dysfunction and diminished blood flow through lungs	Rare—if at all

as such is relatively free from fibrosis unless another or associated process supervenes. Amberson and Spain [3] have described this type of fibrosis as a possible mechanism for the explanation and development of diffuse bullous emphysema: "Chronic organizing constrictive bronchiolitis and peribronchiolitis stiffen the walls and narrow the lumens of the bronchioles and, where the muscular and elastic tissue is damaged and replaced, the mechanism which normally regulates the tonus of the wall and the caliber of the tube was impaired or destroyed. The total effect is an abnormal narrowing of the bronchioles. While inspiratory expansion of contiguous parenchyma will partly open these to permit the passage of air, unusual inspiratory force would be required because of the constricting lesion. In a succeeding expiration the caliber of the bronchioles would be reduced below normal partly because of the constricting lesions and partly because of the loss of musculo-

elastic tonus. This would delay emptying pulmonary lobules which in consequence would be distended."

The physiologic disturbance that results from this type of bronchial or peribronchial fibrosis with the development of obstructive emphysema is essentially ventilatory in character. The main features are a decrease in the vital capacity of the lungs and an increase in the residual air (see table 2). The clinical and functional chain of events that follows depends primarily upon these original disturbances. Diffuse bronchiolectasis may produce the same sequence of events, since the bronchioles that lead directly from the bronchiectatic regions may be narrowed by associated fibrosis. In a study made by the author of 200 consecutive postmortem examinations on cases with varying degrees of bronchiectasis, cor pulmonale was present in 35 instances. In each of the 35 cases where the obstructive emphysema was of a sufficient degree to produce cor pulmonale, a diffuse bronchiolectasis with peribronchiolar fibrosis was present. In those cases where the bronchiectasis was localized rather than diffuse, or where larger bronchi were involved rather than the bronchioles, the obstructive emphysema was never of a sufficiently advanced degree to produce cor pulmonale.

Tuberculosis of the lungs may produce any pattern of fibrosis. Most often several patterns co-exist. However, it is only when bronchiolar or diffuse peribronchiolar fibrosis is present as the result of repeated episodes of bronchogenically disseminated tuberculosis that obstructive emphysema with or without cor pulmonale develops. It is interesting to observe that many of the cases that have developed obstructive emphysema have given histories of repeated episodes of hemoptysis. The blood is an excellent fluid medium for the dissemination of tubercle bacilli diffusely throughout the lungs. Tuberculosis that has spread in this manner may become partially or completely healed with fibrous tissue that is related to bronchioles and, hence, obstructive emphysema results. Observation of numerous cases of chronic pulmonary tuberculosis indicates that it is only in those cases where the above pattern of fibrosis is present that cor pulmonale develops. It is interesting to speculate on what influence the use of streptomycin will have on the residual lesions of tuberculosis. Since streptomycin will undoubtedly alter the course of many cases of pulmonary tuberculosis, we may expect to see in the future many more cases of obstructive emphysema and cor pulmonale developing in tuberculosis.

As stated previously, it is often impossible to correlate quantitatively the degree of fibrosis that occurs with silicosis with the amount of pulmonary or cardiorespiratory disability. However, one can correlate the degree of peribronchiolar fibrosis that occurs in silicosis with the degree of obstructive emphysema. For instance, the fibrosis occurring secondary to asbestosis is more often related to the bronchial tree than in some other forms of silicosis and, hence, it is in this type of silicosis that one sees a higher incidence of emphysema and cor pulmonale. It is not uncommon to see marked

hyalinization and fibrosis in the lungs in a long-standing case of silicosis without any marked disability. These are usually nodular in character. On the other hand, workers exposed to silica in the talc, abrasive soap, and diatomaceous earth industries may develop marked emphysema with disability in a comparatively short period of time and yet quantitatively very little fibrosis may be present. In these cases, the fibrous tissue is found about bronchioles and blood vessels. Once again, it is a question of the pattern of the distribution of the fibrous tissue.

In those cases of Boeck's sarcoid where the infiltration predominantly involves the wall of the bronchus, obstructive emphysema develops. This was illustrated by a recent surgically resected specimen in a case of Boeck's sarcoid on the Chest Division at Bellevue Hospital. The patient was a young female with bilateral nodular consolidation of the lungs. A large emphysematous bulla developed in the right upper lobe. This eventually ruptured and a tension pneumothorax developed. All forms of conservative therapy failed and a lobectomy was finally performed. The specimen revealed diffuse infiltration of the bronchiolar walls with the granulomatous lesions of Boeck's sarcoid. The emphysema and bullae were undoubtedly secondary to this bronchiolar involvement.

Diffuse Interstitial Fibrosis of Alveolar Septa

A second pattern of pulmonary fibrosis is that which occurs in the interstitial tissues of the alveolar septa (see figure 1B). Pure diffuse interstitial fibrosis is not commonly seen. In 1944 Hamman and Rich [4] described several cases in which the fibrosis was predominantly interstitial. They called this condition "acute diffuse interstitial fibrosis of the lungs." The clinical picture varied in duration from several weeks to a few months. All cases ended fatally. Postmortem examination of the lungs in each instance revealed a diffuse interstitial involvement. The changes varied from an interstitial edema and capillary congestion to a chronic inflammatory cell infiltration with fibrosis and thickening of the septa. In some of the cases there was eosinophilic polymorphonuclear cell infiltration. The precapillary arterioles revealed subintimal proliferation and rupture of the elastica. Occasional hyalin membranes were present in the alveoli. There was some mild degree of peribronchiolar fibrosis with associated focal areas of emphysema. The elastic tissue of the alveolar walls was disrupted.

Kneeland and Smetana [5] had previously reported a case of somewhat more acute nature in which the findings were essentially the same. All of these patients suffered from severe respiratory insufficiency. All had marked dyspnea and varying degrees of cyanosis. In one case the cyanosis and right-sided heart failure were quite pronounced. The etiology of this condition is obscure. It is believed by some that it may be related to a form of virus infection.

Several cases of this type, in which diffuse interstitial fibrosis was the predominant change, have been observed at Bellevue Hospital. This change in the lungs was the condition responsible for the main clinical picture and the eventual death of these patients.

Table 3 presents a summary of the age, sex, duration, symptoms at onset, anatomic changes in the lungs, and the degree of hypertrophy of the right ventricle as found in these cases.

It is obvious that, in contrast to the cases reported by Hamman and Rich, there is considerable variation in the duration of these cases, with a range of two months to many years. Whether these are all variations of the same condition related to the same etiologic agent it is impossible to say.

TABLE III

Cases of Diffuse Interstitial Pneumonia with Fibrosis

Age	Sex	Race	Duration	Symptoms and Onset	Thickness of Right Ventricle
66	F	W	7 years	Dyspnea	0.8 cm.
47	F	W	8 months	Dyspnea Cyanosis	10 mm.
59	M	W	1 year	Dyspnea Cyanosis	4 mm.
18	F	N	2½ months	Dyspnea Sore throat Cough	9 mm.
47	M	W	6 months	Exertional dyspnea, upper respiratory infection, cough	11 mm.
34	F	W	?	?	12 mm.
23	M	N	2 months	Cough Dyspnea	4 mm.

The chances are that this is an anatomic change common to different etiologic agents.

There are additional reports in the literature and in textbooks of conditions described as interstitial pneumonia or pneumonitis. Most of these, however, do not conform to the syndrome described by Hamman and Rich, nor are they similar to the briefly described cases in this report. The interstitial pneumonia originally described by MacCallum [6] was supposedly of virus and streptococcal etiology. The anatomic findings, however, indicated that the changes were mainly peribronchiolar rather than limited to the alveolar walls. In the more recent reports of the anatomic findings in primary atypical pneumonia, Parker et al.,[7] Golden,[8] and Karpel et al.,[9] described diffuse interstitial pneumonia in some of their cases where the changes were mainly limited to the alveolar walls. Here again, however, the

majority of the cases reported revealed significant associated predominant changes in the bronchiolar and peribronchiolar regions.

In 1933, McCordock and Muckenfuss [10] reported changes in the lungs of rabbits produced by the injection into the lungs of vaccine virus. He noted that when the vaccine virus was injected in a high concentration, a hemorrhagic edematous consolidation resulted. On the other hand, when this same virus was injected in a dilute form a proliferative lesion was produced in the walls of the bronchi, alveoli and blood vessels that consisted mainly of mononuclear cells. It is a theoretic possibility, therefore, that the entity described by Hamman and Rich, further examples of which are reported here, may be secondary to some form of virus infection in which the virus is present in either lesser concentration or in a less virulent form. However, it must be admitted that this is pure speculation.

Another condition that may be associated with interstitial fibrosis of the lungs is scleroderma. In a small number of cases of scleroderma, there may be associated diffuse changes in the lung which consist primarily of the pattern of fibrosis described above. Such cases have been reported by Matsui,[11] Getzowa,[12] and Spain and Thomas.[13]

As newer industries develop, industrial workers are constantly being exposed to new types of fumes and metallic combinations. Some of these substances on inhalation may possibly produce an interstitial pneumonia that may lead to interstitial fibrosis. This fact must be constantly borne in mind. For instance, experimental work by Highman et al.,[14] indicates that CH_2C1Br, a substance that is a potential substitute for carbon tetrachloride in fire extinguishers, may upon inhalation produce an interstitial pneumonia in mice. Beryllium and bauxite are also some of the substances now known to produce pulmonary changes. In beryllium, the changes are predominantly interstitial, whereas in bauxite they are mainly peribronchial. The anatomic changes in these conditions have been described by Dutra,[15] Johnstone [16] and Hardy.[17]

Congenital alveolar dysplasia of the lungs, the condition recently described by MacMahon,[18] is one in which the alveolar septa are markedly thickened. In this condition the most striking changes are found in the alveolar wall, in which considerable interstitial tissue is present. MacMahon considers this to be a morphologic anomaly, occasionally seen in the lungs of newborn children. He suggests that this anomaly represents a retardation and disturbance in the normal development of pulmonary alveoli. It would seem, however, that this condition possibly represents an infection of the lungs in utero. Since in utero infections must of necessity spread through the circulation rather than through the bronchial tree, the inflammatory changes would be, in all likelihood, predominantly interstitial.

It can be seen, therefore, that the problem of diffuse interstitial changes involving the alveolar walls is one that may become of increasing importance in the evaluation of pulmonary conditions. Interstitial fibrosis that is

limited to the alveolar walls is usually not accompanied by a significant degree of obstructive emphysema. The functional changes are directly related to the thickening of the alveolar wall and the separation of the capillaries in the alveolar septa from the alveolar interface by inflammation, edema and fibrous tissue. Hence, the disturbance is essentially respiratory rather than ventilatory in nature. There is interference with the diffusion of carbon dioxide and oxygen. The resultant anoxia, in addition to exerting a harmful effect systemically, may specifically injure the myocardium (see table 2). Associated with this alveolar wall fibrosis, there is frequently subintimal fibrous proliferation in the smaller arterioles. Whether this is part of the primary process, or secondary to the fact that there is interference with the nutrition of the blood vessel wall, is not clear. At any rate, it will result in a resistance to the flow of blood through the lungs and may eventually produce a strain on the right side of the heart.

In some of the cases of interstitial fibrosis, there were varying degrees of peribronchiolar change. Thus it is possible to have some mild degree of obstructive emphysema present as well.

Fibrosis of Parenchyma (Intra-Alveolar)

Fibrosis of the parenchyma (intra-alveolar) is perhaps the most frequent type of pulmonary fibrosis (see figure 1C). The area of involvement may vary from a few alveoli to an entire lobe or more. It may be localized or diffuse. Very often, not only is the fibrosis confined to the intra-alveolar area but the associated interstitial tissue, blood vessels, and bronchi may be more or less completely obliterated with fibrous tissue. Tuberculosis, suppurative pneumonia, Friedlander's bacillus pneumonia, pneumonia secondary to inhalation of foreign lipoid, or fibrosis following radiation are some of the underlying etiologic agents. In this form of fibrosis, there are occasions when the clinical diagnosis of unresolved pneumonia with organization is made. An unqualified diagnosis of this type is practically never justified, for experience indicates that whenever such a diagnosis is made clinically, further clinical investigation of the case, or eventual verification by postmortem examination, will reveal that the so-called unresolved pneumonia with organization usually turns out to be either a Friedlander's pneumonia, tuberculous pneumonia, pneumonia superimposed upon an unrecognized bronchiectasis, pneumonia secondary to unrecognized bronchial obstruction, either malignant or benign, or else a streptococcus or staphylococcus pneumonia.

Fibrous tissue involves the area to such an extent that it is no longer a functioning unit. The important associated secondary change is distention emphysema. This occurs in the adjacent lung parenchyma or, if an entire lobe is involved, in the adjacent lobe or contralateral lung. Functional disturbances, therefore, are directly proportional to the amount of lung tissue involved and to the degree of distention emphysema that develops (see

table 2). In a sense, the disturbance is analogous to some of the changes one might expect to find following surgical removal of varying portions of lung tissue. Since the lung has considerable reserve, moderate degrees of parenchymal fibrosis usually produce no significant functional changes. When such changes do occur, they are not necessarily directly related to the amount of lung replaced by fibrous tissue, but are more often related to the associated secondary change in the remaining functioning lung parenchyma, namely, distention emphysema. To what extent significant impairment of function may result from distention emphysema is not entirely clear. Whether long-standing distention emphysema might eventually become converted into a diffuse obstructive emphysema is also not definitely known. In silicosis, for instance, there are cases that show marked fibrous replacement of the lung parenchyma and yet have very little evidence of pulmonary insufficiency. On the other hand, there are other examples of patients with silicosis in whom fibrosis is quantitatively less in amount than in the above cases but is distributed in a finely nodular and diffuse pattern. In these cases, the patients often have an advanced degree of ventilatory impairment. In the former cases, the fibrosis is essentially parenchymal, while in the latter, the fibrosis, although limited in amount, is strategically located in relation to the bronchial tree.

Fibrosis of the Pulmonary Vascular Bed

Fibrosis of the pulmonary vascular bed perhaps in a strict sense should not be included in a discussion of pulmonary fibrosis (see figure 1D). However, in order fully to appreciate the various patterns of fibrosis as related to the different disease entities involving the lung, it is necessary to include this form. Furthermore, on occasion when a clinical roentgenologic diagnosis of diffuse fibrosis of the lung has been made, postmortem examination has revealed changes which were confined almost entirely to the pulmonary vascular bed. A case in point was that of a middle-aged white male morphine addict whose main complaint on admission to the hospital was dyspnea. A roentgen-ray picture of the lungs was interpreted as showing diffuse pulmonary fibrosis. The patient eventually died of congestive heart failure which was mainly right-sided in its manifestations. At postmortem examination, innumerable foreign body emboli were found in the pulmonary arterioles. Foreign body reactions were present at these points, both in and around the vascular channels. Many of the pulmonary arterioles contained thrombi that were in various states of organization and canalization. The right ventricle of the heart was hypertrophied and the chamber was dilated. The antecubital veins contained organized thrombi, and the overlying skin revealed numerous pitted scars. It was known that this patient had inoculated himself intravenously on many occasions with narcotics. During some of these episodes of self-inoculation (the technic was undoubtedly nonsterile), foreign material was introduced into the circulation. This pro-

duced a fibrotic pattern related to the pulmonary vascular tree. The disability that results from such an anatomic disturbance is quite obvious. There is a diminution of the pulmonary vascular bed and, hence, an increase in the resistance to the flow of blood through the lungs.

Such conditions as multiple pulmonary arteriolar emboli with organization and canalization, schistosomiasis of pulmonary vessels, primary pulmonary arteriolarsclerosis, endolymphatic carcinomatosis, the infrequent occurrence of periarteritis of pulmonary vessels, may all produce similar sclerotic changes in the vascular walls. On occasion, some forms of congenital heart disease—in particular, patent ductus arteriosus—may produce an advanced form of pulmonary arteriosclerosis and arteriolarsclerosis (Welch and Kinney [19]). This usually occurs in those patients having an exceptionally large volume of blood flow through the patent ductus. It is most often seen in patients in the third or fourth decade of life. The pulmonary hypertension that develops secondary to these changes may at times exceed the tension of the systemic circuit and even cause a reversal of the flow of blood through the ductus.

Some have described changes in the lungs of patients with long-standing chronic passive congestion secondary to mitral stenosis. These changes consisted of thickening of the vascular walls and an increase in the interstitial tissue of the lungs. Von Glahn and Hall [20] have experimentally produced foreign body reactions in and about the pulmonary vascular bed by the injection of cotton fibers into the circulation of rats. These changes were somewhat similar to those described in the case of the narcotic addict.

The most frequent form of sclerosis involving the pulmonary arterioles is secondary to pulmonary hypertension itself. This pulmonary hypertension is most frequently associated with diffuse obstructive emphysema.

As has been previously mentioned, in silicosis the pattern of fibrosis may be both parenchymal and bronchial. It also may be to a great extent vascular. Geever [21] has recently described in great detail extensive fibrotic and necrotic changes produced by silicosis in the pulmonary vascular bed. As industries develop technics and products with finer and finer silica particles, one may expect to see interstitial fibrosis secondary to silica as well.

The effect of the changes in flow of blood through the pulmonary vascular bed in relation to respiratory and ventilatory disturbances is only inadequately understood. The exact extent of blood flow, the size of the vascular bed, and the presence or absence of shunts can be only roughly conjectured in any particular condition. Until these factors can be determined with some degree of accuracy, it will be impossible to explain some of the discrepancies that exist between anatomic and functional observations.

Involvement of the pulmonary vascular bed, however, obviously will produce some degree of pulmonary hypertension, to some extent impair the nutrition of the lung, and also to some extent produce diffusion disturbances (see table 2).

Fibrosis of the Pleura

The fifth form of fibrosis is that related to the pleura (see figure 1E). This may result from the organization of the exudate which develops secondary to acute and chronic pyogenic empyema, tuberculous empyema, or trauma with blood in the pleural space. The fibrinous, serofibrinous, or fibrinopurulent exudate present in these conditions becomes organized and a fibrotic pleural envelope develops which contracts and constricts the lung parenchyma. This eventually interferes with both the ventilatory capacity of the lung and also with the flow of blood through the involved area. The secondary effect is that of the development of distention emphysema in the uninvolved portions or in the contralateral lung. Sometimes, in extensive pleural fibrosis, fibrous tissue may extend along the interlobular septa into the lung parenchyma. This has the further effect of diminishing the elasticity of that particular portion of the lung. This in turn further interferes with the ventilatory capacity (see table 2).

With the development of new surgical technics whereby these fibrotic pleural envelopes may be removed and the lung reëxpanded, it has become increasingly important to determine the amount of return to normal function that may occur after reëxpansion of a long-standing compressed lung. Present studies seem to indicate that complete restoration of function does not occur despite apparent complete anatomic reëxpansion. This may be accounted for by the fact that most cases with fibrotic pleural envelopes also have underlying pulmonary disease. Perhaps the best cases for a study of this sort would be those cases in which the fibrotic pleural envelope had developed secondary to blood in the pleural space and in which there was no underlying pulmonary disease. The reëxpansion of the lung will, of course, prevent the progression of distention emphysema in the contralateral lung.

Relationship of Fibrosis of the Lungs to Cor Pulmonale

It is not within the scope of this report to discuss the causes of cor pulmonale. However, insofar as cor pulmonale is most often a direct consequence of pulmonary change, it is of interest to note the relationship of pulmonary fibrosis to this development.

A perusal of table 4, which lists the causes of cor pulmonale as observed in 100 postmortem examinations, indicates that fibrosis of the vascular bed is only infrequently a direct cause of pulmonary hypertension. It can be seen that emphysema, bronchiectasis, bronchial asthma, tuberculosis, and silicosis are responsible for about 80 per cent of the cases of cor pulmonale. In these conditions, fibrosis is not primarily related to the vascular bed (Spain and Handler).[22] The fibrous tissue primarily involves the bronchial walls, and it is through the resultant emphysema that cor pulmonale develops. The exact mechanisms for the development of pulmonary hypertension in emphysema are still not indisputably proved. However, such

factors as reduction in the vascular bed, increased pleural and alveolar tension, reduction in alveolar oxygen content, polycythemia, etc., all probably play a rôle. Fibrosis of the vascular bed on certain occasions, however, is a

TABLE IV

Underlying Conditions in 100 Necropsied Cases of Cor Pulmonale

Underlying Pulmonary Conditions	Number of cases
Emphysema	51
Bronchiectasis	9
Bronchial asthma	6
Silicosis and silicotuberculosis	6
Tuberculosis	6
Kyphoscoliosis	1
Thoracoplasty and tuberculosis	5
Primary pulmonary arteriolarsclerosis	1
Diffuse interstitial fibrosis	5
Schistosomiasis	1
Foreign body emboli (morphine addiction)	1
Multiple pulmonary emboli with organization	2
Pulmonary artery thrombosis	2
Scleroderma	1
Boeck's sarcoid	2

direct cause for the pulmonary hypertension. These have been referred to previously in the discussion of fibrosis of the pulmonary vascular bed and may be again noted in table 4.

SUMMARY AND CONCLUSIONS

1. The lack of correlation between subjective and objective clinical findings of disturbed pulmonary function with the degree of fibrosis seen on the roentgenogram may, to a great extent, be resolved by an evaluation of the pattern of fibrosis rather than by the degree of fibrosis.

2. Fibrosis of the lungs may occur in five distinct patterns: bronchial, interstitial, parenchymal, pleural, and vascular. These patterns may often co-exist.

3. The different patterns will to a great extent determine the type of functional disability. Bronchial fibrosis will produce functional changes associated with diffuse obstructive emphysema. Interstitial fibrosis will produce essentially diffusion disturbances. Vascular fibrosis will produce pulmonary hypertension. Pleural fibrosis will produce some degree of ventilatory disturbance, as will advanced degrees of parenchymal fibrosis.

4. Diffuse interstitial fibrosis of the lung produces a distinct clinical pathologic syndrome. This entity is becoming more important and is more frequently recognized. It may possibly be related to some form of virus infection.

5. Pulmonary fibrosis is most often only indirectly related to the development of pulmonary hypertension.

BIBLIOGRAPHY

1. Reisner, D.: Boeck's sarcoid and systemic sarcoidosis, Am. Rev. Tuberc. **49**: 289–307 (April) 1944.
2. Baldwin, E., Cournand, A., and Richards, D.: Personal communication. To be published.
3. Amberson, J. B., and Spain, D. M.: A mechanism explaining chronic progressive pulmonary bullous emphysema, Tr. A. Am. Physicians **60**: 92–101, 1947.
4. Hamman, L., and Rich, A. R.: Acute diffuse interstitial fibrosis of the lungs, Bull. Johns Hopkins Hosp. **74**: 177–212, 1944.
5. Kneeland, Y., Jr., and Smetana, H. F.: Current bronchopneumonia of unusual character and undetermined etiology, Bull. Johns Hopkins Hosp. **67**: 229–267, 1940.
6. MacCallum, W. G.: A textbook of pathology, 3d ed., 1924, W. B. Saunders Co., Philadelphia, 514–516.
7. Parker, F., Jr., Jollife, L. S., and Finland, M. J.: Primary atypical pneumonia, Arch. Path. **44**: 581–608 (Dec.) 1947.
8. Golden, A.: Pathologic anatomy of "atypical pneumonia etiology undetermined": acute interstitial pneumonitis, Arch. Path. **38**: 187–202 (Oct.) 1944.
9. Karpel, S., Waggoner, I. M., and McCown, O. S., Jr.: Primary atypical pneumonia—a critical analysis of 500 cases, Ann. Int. Med. **22**: 408–417 (Mar.) 1945.
10. McCordock, R. S., and Muckenfuss, R. S.: Similarity of virus pneumonia in animals to epidemic influenza and interstitial bronchopneumonia in man, Am. J. Path. **9**: 221–252 (Mar.) 1933.
11. Matsui, S.: Ueber die Pathologie und Pathogenese von Sclerodermia universalis, Mitteilungen aus der Medizin, Fakultaet der Kaiserl., Univ. Tokyo **31**: 55–116, 1924.
12. Getzowa, S.: Cystic and compact pulmonary sclerosis in progressive scleroderma, Arch. Path. **40**: 99–106 (Aug.) 1945.
13. Spain, D. M., and Thomas, A.: The pulmonary manifestations of scleroderma: an anatomic-physiological correlation, Ann. Int. Med. **32**: 152–161, 1950.
14. Highman, B., and Swebely, J. L.: Pathologic changes produced by monochloromonobromomethane (CH_2ClBr), Arch. Path. **45**: 299–310 (Mar.) 1948.
15. Dutra, F. R.: The pneumonitis and granulomatosis peculiar to beryllium workers, Am. J. Path. **24**: 1137–1165 (Nov.) 1948.
16. Johnstone, R. T.: Pulmonary affections of occupational origin, Am. Rev. Tuberc. **58**: 375–392 (Oct.) 1948.
17. Hardy, H. L.: Beryllium pneumonitis, Am. Rev. Tuberc. **57**: 547–556 (June) 1948.
18. MacMahon, H. E.: Congenital alveolar dysplasia of lungs, Am. J. Path. **24**: 919–931 (July) 1948.
19. Welch, K. J., and Kinney, T. D.: The effect of patent ductus arteriosus and of interauricular and interventricular septae defects on the development of pulmonary vascular lesions, Am. J. Path. **24**: 729–761 (July) 1948.
20. Von Glahn, W. C., and Hall, J.: Personal communication. To be published.
21. Geever, E. F.: Pulmonary vascular lesions in silicosis and related pathologic changes, Am. J. M. Sc. **214**: 292–304 (Sept.) 1947.
22. Spain, D. M., and Handler, B.: Chronic cor pulmonale, Arch. Int. Med. **77**: 37–65 (Jan.) 1946.

CYTOLOGY OF SPUTUM AND BRONCHIAL SECRETIONS: STUDIES ON 588 PATIENTS WITH MISCELLANEOUS PULMONARY LESIONS *

By LEWIS B. WOOLNER, M.D., and JOHN R. MCDONALD, M.D.,
Rochester, Minnesota

A NUMBER of investigators have shown that bronchogenic carcinoma may be diagnosed by cytologic examination of sputum or bronchial secretions.[1, 2, 3, 4, 5, 6, 7, 8] These preliminary studies have been, in the main, enthusiastic, but much remains to be learned concerning the use of the method in practice. Of particular importance is the question whether cytologic technic may be used advantageously more or less as a screening device in the routine diagnostic procedures of a general chest service. The present paper deals with our experience with the method as a routine procedure in the investigation, over a given period, of all patients with suspected pulmonary neoplasm.

In the authors' laboratory, cytologic studies have been carried out over a period of almost three years, during which time a total of 325 cases of bronchogenic carcinoma have been diagnosed by examination of sputum or bronchial secretions. The results of the first 300 cases have been published in two series of 150 cases each.[9] The accuracy of diagnosis as regards false positive reports has been very satisfactory. During the first series of 150 cases, three proved false positive diagnoses were given and in two additional cases the final diagnosis, whether inflammatory or neoplastic, was not established. In the second series of 150 cases, only one proved false positive report was given.

In order to evaluate the number of false negative examinations on cases of bronchogenic carcinoma, all cases in which cytologic examination was performed over a given period were selected. This period coincided with our last 100 positive cases. During this time, sputum or bronchial secretions were examined on 588 patients. All of these presented symptoms related to the chest, and the majority showed roentgenographic pulmonary shadows.

TECHNIC

Details of collection, smearing and fixation of specimens have been published in previous articles by the authors.[10, 11] Briefly, five smears are prepared from each specimen. These are fixed while wet in equal parts of

* Read at the Regional Meeting of the American College of Physicians, Detroit, Michigan, November 20, 1948.
Received for publication November 27, 1948.
From the Division of Surgical Pathology, Mayo Clinic, Rochester, Minnesota.

alcohol and ether according to the method of Papanicolaou.[12] The staining technic used is hematoxylin and eosin. Very adequate cell detail can be obtained in this way (figure 1). All specimens are examined as unknowns and reported as positive or negative for carcinoma cells. Repeat specimens are requested in cases which show some atypical cells but in which insufficient evidence is present on which to base a definite diagnosis. The time required for examination of a slide varies from six to 10 minutes, so that on the average 30 to 50 minutes are required for a negative case. In practice, a large part of the scanning of slides can be carried out by well-trained technicians, but the final diagnosis on all cases is done by the pathologist.

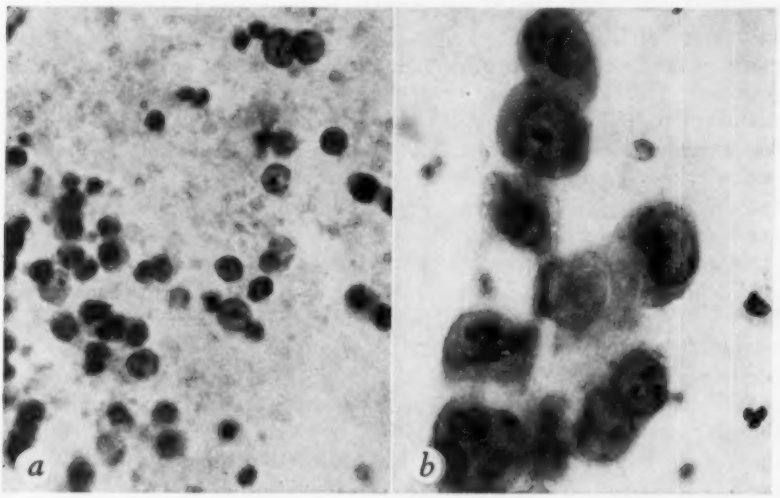


FIG. 1. Carcinoma cells in sputum. *a*. Carcinoma cells in sputum from a small-celled "oat cell" bronchogenic carcinoma (hematoxylin and eosin × 750). Note the variation in size of nuclei and absence of cytoplasm. *b*. Carcinoma cells in sputum from an undifferentiated large-cell bronchogenic carcinoma. Note the large size of nuclei and prominent nucleoli (× 750).

As with examination of sputa for tubercle bacilli, it is desirable in many cases to examine more than one specimen for malignant cells. In this series of 588 cases, a total of 882 sputum specimens were examined, an average of 1.5 per patient. In addition, bronchial secretions were examined on 245 patients. It is recommended that three sputa, if necessary, be studied on a given case before one considers that an adequate cytologic examination has been carried out. The additional time required for examination of sputum in contrast to bronchial secretions is somewhat offset by the ease of obtaining additional specimens, a very important consideration if few atypical cells are present and more evidence is required on which to base a positive diagnosis.

Accuracy of Diagnosis by Smear Technic

In this series of 588 cases in which cytologic examination was carried out, the final clinical diagnosis was as follows: bronchogenic carcinoma, 147 cases; indeterminate, probably non-neoplastic, 39 cases; probable metastatic carcinoma of lung, 30 cases; adenoma of the bronchus, five cases; non-neoplastic pulmonary disease (tuberculosis, bronchiectasis, and so forth), 367 cases.

Of 147 cases of proved or strongly suspected bronchogenic carcinoma, a positive cytologic diagnosis was made in 100 cases, representing 68 per cent positive findings. No known false positive reports were given in this series. The number of sputa examined in the positive cases totaled 161, or an average of 1.6 per patient. In 75 per cent of cases the diagnosis was made on the first specimen submitted; in the remainder, two or more were required. Of the 47 cases of bronchogenic carcinoma missed by cytologic examination (false negatives), a single bronchial secretion, but no sputum, was examined in seven; in 21 cases, sputum examination alone was carried out, with an average of two specimens per patient, and in 19 cases both sputum and bronchial secretions were examined, averaging 2.3 sputa and one bronchial secretion on each.

A comparison of the results of bronchoscopic examination and cytologic studies in this group reveals a much lower rate of positive bronchoscopic biopsy than positive cytologic findings. Of these 147 consecutive patients with bronchogenic carcinoma, 93 underwent bronchoscopic examination. A positive biopsy was obtained in 38 of these (41 per cent). Cytologic studies on these 93 patients were positive in 65 cases (70 per cent). Of the 47 cases of bronchogenic carcinoma in this series in which cytologic findings were negative (false negatives), a bronchoscopic examination was done in 28 cases. A positive biopsy was obtained in one case.

Surgical Procedures. Of the 147 patients with bronchogenic carcinoma in this series, 48 underwent surgical exploration. Of these, both smears and bronchoscopic biopsy were positive in 21 cases, smears alone were positive in 12, and both smears and biopsy were negative in 15 cases.

In a total of 29 cases, lobectomy or pneumonectomy was carried out. Of these, both biopsy and smears were positive in 11 cases, smears alone were positive in nine cases, and both smears and biopsy were negative in nine cases.

In summary, of 48 cases in which exploration was performed for bronchogenic carcinoma, smears were positive in 33 cases (69 per cent), while the biopsy was positive in 21 (44 per cent). Similarly, of 29 cases in which resection for bronchogenic carcinoma was carried out, smears were positive in 20 (69 per cent), while the biopsy was positive in 11 (38 per cent).

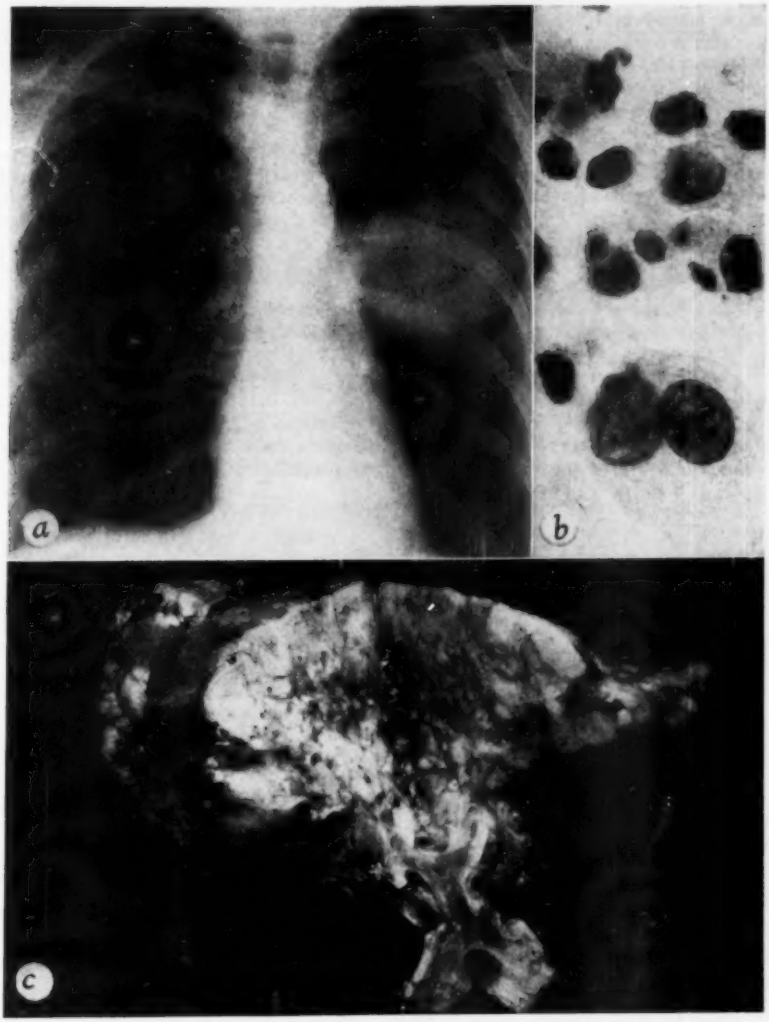


FIG. 2. Bronchogenic carcinoma with negative bronchoscopic biopsy. *a*. Roentgenogram of chest showing large tumor next to the hilus. *b*. Carcinoma cells found in the sputum (×750). *c*. Surgically removed lung showing large bronchogenic carcinoma in upper lobe.

Illustrative Cases In Which The Diagnosis Of Bronchogenic Carcinoma Was Made By Cytologic Studies

To emphasize the value of cytologic technic in routine diagnosis of chest diseases a few cases will be outlined in some detail.

Case Reports

Bronchogenic Carcinoma. Clinically and Roentgenographically—Bronchoscopic Biopsy Negative. A woman, aged 65 years, had complained of a cough with some pain in the left side of the chest for 16 months. Slight hemoptysis had been noted on one occasion. Three months before admission a roentgenogram of the chest had been taken at a mobile unit. Two months later she received a letter telling her to go to her local physician because of a nontuberculous chest lesion. Three weeks later, a diagnosis of "lung tumor" was made.

On admission, a roentgenogram of the chest revealed a large tumor adjacent to the hilus, probably bronchogenic carcinoma (figure 2*a*). Sputum studies were positive for carcinoma cells (figure 2*b*). Bronchoscopic examination revealed a tumor mass arising from the left upper lobe bronchus, but the biopsy specimen taken proved to be non-neoplastic. Bronchial smears were negative.

Left pneumonectomy was carried out. Pathologic examination revealed a large bronchogenic carcinoma of the upper lobe with involvement of a fairly small bronchus (figure 2*c*). The postoperative course was uneventful.

Bronchogenic Carcinoma with Negative Roentgenogram of the Chest. In three cases encountered, a routine roentgenogram of the chest was negative and the sputum was found positive for carcinoma cells.

In one of these, the patient had had a cough for two months and showed evidence of superior vena caval obstruction. No bronchoscopic examination could be carried out because of a suspected ruptured intracranial aneurysm five years before. The final diagnosis was bronchogenic carcinoma with superior vena caval involvement.

In the second case with an essentially negative roentgenogram and carcinoma cells in the sputum, bronchoscopy was performed and a nodular ulcerative lesion at the orifice of the left main bronchus was demonstrated. The gross appearance was that of carcinoma. Roentgenographic changes in the lung typical of bronchogenic carcinoma developed before death three months later.

In the third case, in which a routine roentgenogram of the chest was essentially negative and the sputum was found positive for carcinoma cells, it was eventually shown by tomogram that there was an irregularity of the left upper lobe bronchus. Pneumonectomy revealed a very small bronchogenic carcinoma of the upper lobe with one regional lymph node involved.

Carcinoma of the Lungs Simulating Tuberculosis. That bronchogenic carcinoma may masquerade as tuberculosis is shown by a study of five cases of this series, three of which are briefly described.

Case 1. This patient had no symptoms referable to his chest except slight pain in the left axilla for two days and minimal hemoptysis the day before admission. A roentgenogram revealed a pathologic process in the left apex, probably tuberculosis. Although his clinical picture suggested an infective process, sputum studies were positive for carcinoma cells. On this finding the lung was removed surgically and a small bronchogenic carcinoma, 2 cm. in diameter, was found in the apex.

Case 2. In this case, the patient's symptoms extended back to an attack of "virus pneumonia" three years before admission. For two years he had noted slight hemoptysis after hard coughing, and he had lost 20 pounds (9.1 kg.). The results of fairly extensive sputum studies for tubercle bacilli carried out about two years before had been negative. On admission examination, the clinical impression was pulmonary tuberculosis. A roentgenogram of his chest revealed "tuberculosis of the right upper lobe with considerable fibrosis and fairly marked right apical pleuritis with depression of the apical portion of the right lung. The tuberculous process is active" (figure 3*a*). In spite of the clinical and roentgenographic findings, smears and cultures of sputum were negative for tubercle baeilli, as were gastric cultures. The results of a sputum

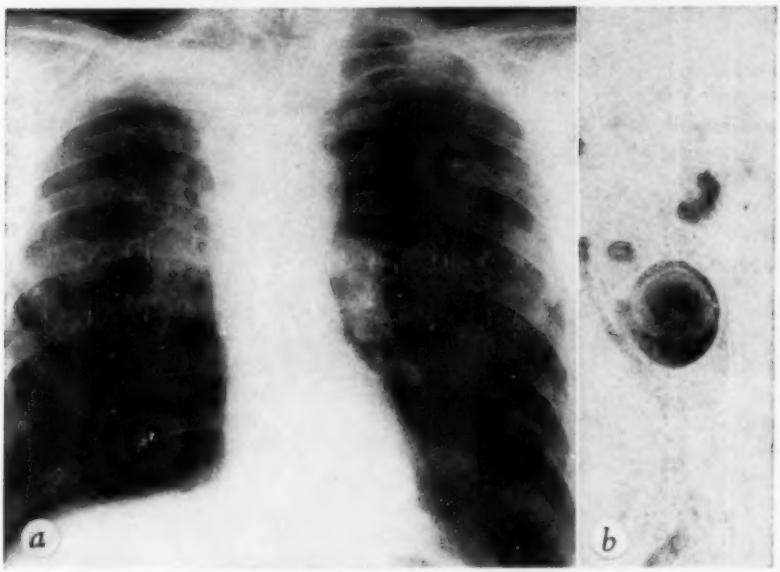


FIG. 3. Bronchogenic carcinoma simulating tuberculosis. *a.* Roentgenogram of chest interpreted as active tuberculosis of right upper lobe. *b.* Carcinoma cells found in the sputum. Epithelial pearl indicating the presence of a squamous-cell epithelioma. Bronchoscopic biopsy showed a squamous-cell bronchogenic carcinoma.

examination for malignant cells done at this time were positive (figure 3*b*). Bronchoscopic examination was then carried out, and an infiltrating lesion of the right main bronchus was demonstrated. Biopsy revealed a squamous-cell carcinoma, confirming the sputum findings. The condition was inoperable because of involvement of the posterior wall of the trachea.

Case 3. This patient, a man 64 years of age admitted for a minor complaint, had no symptoms referable to his chest. A routine roentgenogram at this time, however, revealed a "lesion in the upper lobe of the left lung. Active tuberculosis until proved otherwise." Further tests were advised but the patient did not remain for investigation of the chest lesion. He was advised to have monthly observations of the pulmonary lesion. Roentgenograms taken three months and six months later revealed no

significant change. Further studies at this time revealed negative sputum cultures for acid-fast bacilli; the results of skin tests were positive for tuberculin but negative for histoplasmin and coccidioidin. The patient still had no chest symptoms, and his general health had improved. A roentgenogram of the chest nine months after initial examination showed the lesion on the left to be about twice as extensive, with a

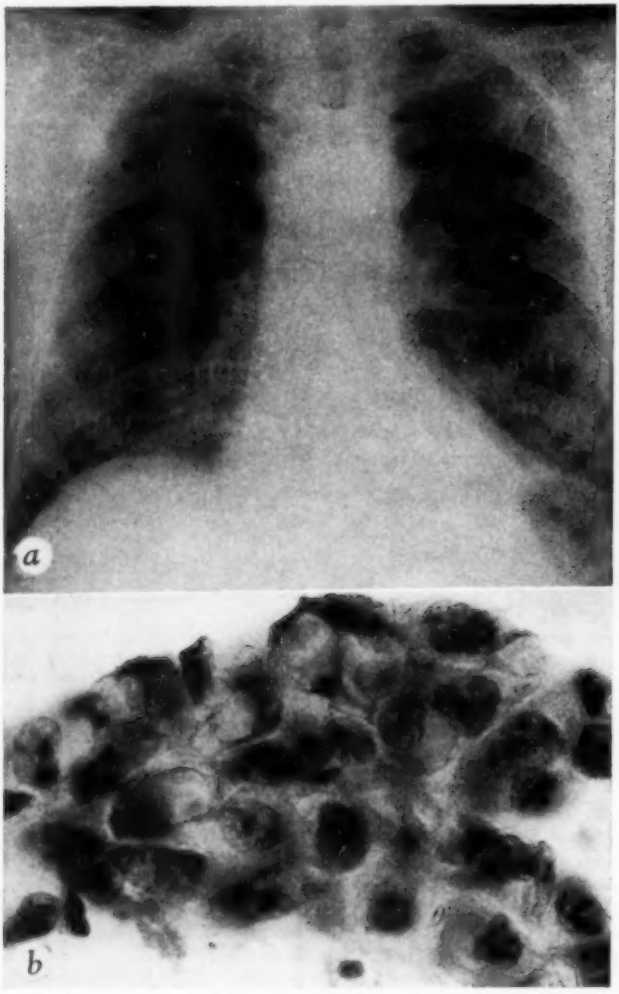


FIG. 4. Bronchogenic carcinoma simulating tuberculosis. *a*. Final roentgenogram of chest showing bronchogenic carcinoma in the left upper lobe with spread to the right lung. Previous roentgenograms had been interpreted as tuberculosis. *b*. Large clump of closely packed carcinoma cells found in the sputum in this case (hematoxylin and eosin × 750).

minimal lesion in the right upper lobe. The roentgenographic diagnosis was active tuberculosis. One year after his initial roentgenogram, he returned for further investigation. He still had no pulmonary symptoms but had roentgenographic evidence of spread to the right lung and hilar adenopathy (figure 4*a*). The roentgenographic interpretation was a pulmonary malignant lesion on the left with spread to the right lung. Sputum studies for malignant cells were now carried out for the first time and their results were positive (figure 4*b*). Two further roentgenograms of the chest at weekly intervals were diagnosed as showing pulmonary malignancy. A bronchoscopic examination was carried out and was negative. The bronchoscopist could not see beyond the orifice of the bronchus of the left upper lobe. The final diagnosis, based on the roentgenographic appearances and the findings of carcinoma cells in the sputum, was bronchogenic carcinoma. This condition was inoperable because of the spread to the opposite lung.

In two other cases in which roentgenograms of the chest suggested tuberculosis, no tissue proof was obtained, but the presence of exfoliated cancer cells in the sputum provided convincing evidence that the lesions in question were neoplastic.

In all the foregoing cases the roentgenographic interpretation of the lesion was that of pulmonary tuberculosis. However, no tubercle bacilli could be demonstrated by smear, culture, or animal inoculation. In such cases, as with all indeterminate lesions of the chest, it is obviously important to include cytologic examination of the sputum or bronchial secretions for malignant cells as a part of the routine investigation of the patient.

Pancoast's Superior Sulcus Tumor. Tumors of the pulmonary apex or superior sulcus tumors constitute a highly inaccessible group of neoplasms. All of these are inaccessible to bronchoscopic biopsy. Too frequently the diagnosis is not established until erosion of ribs or involvement of the brachial plexus renders the condition inoperable. Examination of sputum or bronchial secretions in this group of tumors will frequently yield positive results. In this series, Pancoast's tumor was diagnosed in eight cases, five of which were diagnosed correctly by the presence of carcinoma cells in sputum or bronchial washings. Bronchoscopic examination was carried out in only two cases, both of which were negative. In three cases, sputum was examined and found negative. No bronchial secretions or washings were obtained on any of the missed cases. The number of sputa examined was adequate in only one of these three patients. In two cases, the lung was removed surgically. In one of these the tumor mass was found directly beneath the apical pleura posteriorly and complete removal was possible. In the other instance, although the lung was removed, it was felt that some infiltration of structures of the chest wall had already taken place.

Alveolar-Cell Carcinoma. In our previous experience, four cases of so-called alveolar-cell carcinoma have been diagnosed by cytologic examination of sputum or bronchial secretions. In this series, three additional cases were encountered. In one case, outlined in the next paragraph, a diagnosis of carcinoma was first indicated by the cytologic findings in the sputum. In two others, unusual cells were found in the sputum but these were not suf-

ficiently atypical to warrant a definite cytologic diagnosis. In both of these cases exploration was performed; lobectomy was done in one case and pneumonectomy in the other. In both, the histologic picture was that of so-

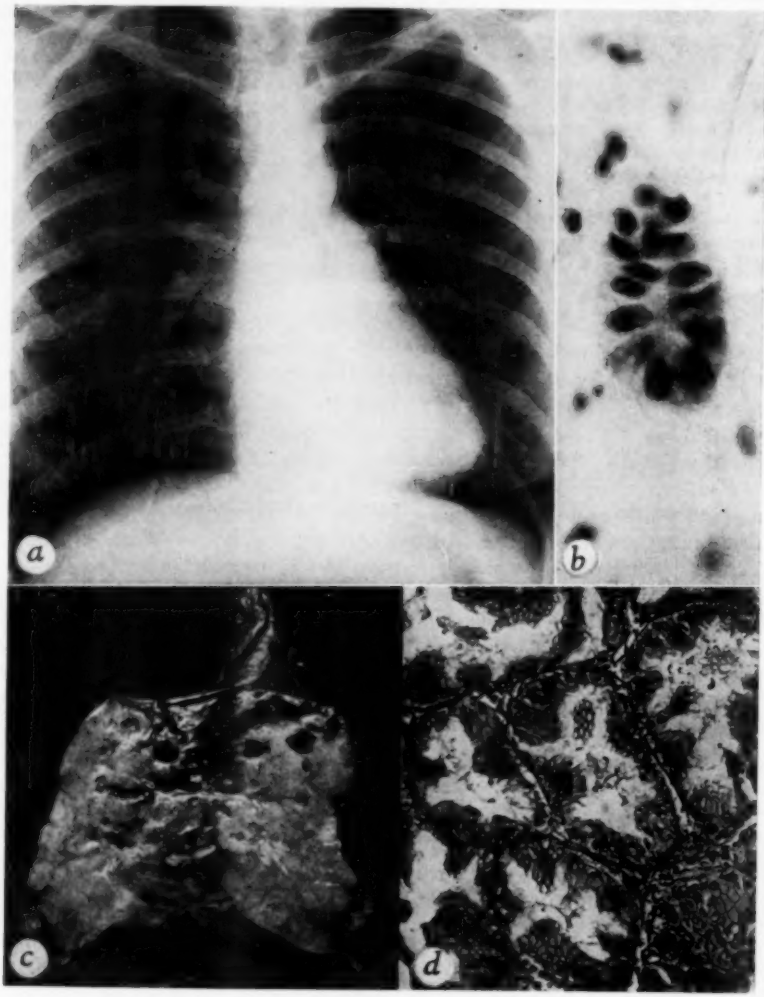


FIG. 5. "Alveolar-cell carcinoma" of left lower lobe with positive cytologic findings. *a*. Roentgenogram of chest showing lesion located posteriorly in the lower portion of the left lung, "probably neoplastic in nature." Parenchymal infiltration in right midlung field. *b*. Carcinoma cells found in sputum (×750). *c*. Gross appearance of surgically removed left lower lobe: alveolar-cell carcinoma. *d*. Histologic section of tumor.

called alveolar-cell carcinoma. The case in which sputum studies were definitive for carcinoma is outlined briefly.

A woman, aged 30 years, began to have a productive cough one year before admission. This continued for three months with fever and night sweats. A roentgenogram of the chest at this time showed shadows suggestive of tuberculosis. On this basis she was admitted to a tuberculosis sanatorium, where she remained four months. Her cough continued and slight hemoptysis developed with afternoon fever, easy fatigability, exertional dyspnea, and left lower chest pain on deep inspiration. Investigation at the sanatorium failed to confirm the diagnosis of tuberculosis. The Mantoux reaction was negative. The patient was sent home. On examination at the Mayo Clinic, a roentgenogram of the chest revealed an "infiltrating lesion located posteriorly in the left lower lung probably neoplastic in nature. There is also parenchymal infiltration in the right midlung field" (figure 5*a*). Sputum was examined for malignant cells and found to be positive (figure 5*b*). Bronchoscopic examination failed to show any gross evidence of tumor. Saline washings were obtained from the posterior basal division of the left lower lobe. A biopsy was taken from the depths of this division and reported "grade 1 papillary adenocarcinoma, consider alveolar-cell carcinoma." Carcinoma cells, however, were found present in both right and left bronchial secretions. Since the roentgenographic appearance of the right lung had not changed materially in the previous 10 months, it was decided that left lower lobectomy should be done. This was carried out and on pathologic examination an alveolar-cell carcinoma, multiple nodular type, involving the greater portion of this lobe was found (figure 5*c*). The largest nodule was 2 cm. and the smallest 0.2 cm. in diameter. Histologic section of the tumor is shown in figure 5*d*. The status of the right lung is at present undetermined.

Summary

In a group of 588 cases of miscellaneous chest diseases, in which a routine cytologic examination of sputum or bronchial secretions was carried out, 147 cases of proved or suspected bronchogenic carcinoma occurred. Of these 147 cases, 100 (68 per cent) were detected by a cytologic examination of sputum or bronchial secretions. No known false positive diagnoses occurred in this series. Of 93 patients with bronchogenic carcinoma who underwent bronchoscopic examination, a positive biopsy was obtained in 38 (41 per cent). In this same group, cytologic studies were positive on 65 patients (70 per cent).

BIBLIOGRAPHY

1. Dudgeon, L. S., and Wrigley, C. H.: On the demonstration of particles of malignant growth in the sputum by means of the wet-film method, J. Laryngol. and Otol. **50**: 752–762, 1935.
2. Barrett, N. R.: Examination of sputum for malignant cells and particles of malignant growth, J. Thoracic Surg. **8**: 169–183, 1938.
3. Gowar, F. J. S.: Carcinoma of the lung: the value of sputum examination in diagnosis, Brit. J. Surg. **30**: 193–200, 1943.
4. Wandall, H. H.: A study on neoplastic cells in sputum as a contribution to the diagnosis of primary lung cancer, Acta chir. Scandinav. **91**: (suppl. 93), 1–143, 1944.
5. Herbut, P. A., and Clerf, L. H.: Bronchogenic carcinoma; diagnosis by cytologic study of bronchoscopically removed secretions, J. A. M. A. **130**: 1006–1012, 1946.

6. Papanicolaou, G. N.: Diagnostic value of exfoliated cells from cancerous tissues, J. A. M. A. **131**: 372–378, 1946.
7. McKay, D. G., Ware, P. F., Atwood, D. A., and Harken, D. E.: The diagnosis of bronchogenic carcinoma by smears of bronchoscopic aspirations, Cancer **1**: 208–222, 1948.
8. Liebow, A. A., Lindskog, G. E., and Bloomer, W. E.: Cytological studies of sputum and bronchial secretions in the diagnosis of cancer of the lung, Cancer **1**: 223–233, 1948.
9. Woolner, L. B., and McDonald, J. R.: Cytologic diagnosis of bronchogenic carcinoma, Am. J. Clin. Path. **19**: 765–769, 1949.
10. Woolner, L. B., and McDonald, J. R.: Symposium on identification of carcinoma cells in sputum, bronchial secretions and urine. Bronchogenic carcinoma: diagnosis by microscopic examination of sputum and bronchial secretions; preliminary report, Proc. Staff Meet., Mayo Clin. **22**: 369–381, 1947.
11. Woolner, L. B., and McDonald, J. R.: Carcinoma cells in sputum and bronchial secretions: a study of 150 consecutive cases in which results were positive, Surg., Gynec. and Obst. **88**: 273–290, 1949.
12. Papanicolaou, G. N.: A new procedure for staining vaginal smears, Science **95**: 438–439, 1942.

CRITERIA FOR AND INTERPRETATION OF NORMAL GLUCOSE TOLERANCE TESTS*

By HERMAN O. MOSENTHAL, M.D., F.A.C.P., and EILEEN BARRY, B.S.,
New York, N. Y.

THE old dictum that every diabetic has a high prolonged glucose tolerance curve, but that every high prolonged curve is not indicative of diabetes, still holds true. The lack of specificity of the crucial test often puts an unwarranted mental, physical, and financial burden upon the individual suspected of diabetes. It has been the purpose of our studies to approach the true conditions a little more closely and to make the procedure more definite. Preliminary publications of these observations have been made.[1] They were largely on diabetic patients, while the present effort concerns itself solely with normal individuals. Fifty tests were carried out. The subjects were from all classes of society. They were divided roughly into three age groups: those under 40, those from 40 to 60, and those in the old age category, over 60. Only ambulant persons were used. We heeded the discovery of Blotner[2] that bed rest diminished the normal response to glucose and, as a result, we believe we have shown that no impairment of tolerance occurs in the aged who are up and about and not confined to a home or bedridden.

All tests were made in duplicate, two on venous and one on arterial (capillary) blood. The methods for the sugar values in venous blood were the generally used Folin-Wu[3] procedure, which includes a variable amount of nonglucose reducing substances, and one in which nonglucose substances were eliminated and the "true blood sugar" determined. The latter differs from the Folin-Wu procedure in that the blood precipitant used preparatory to filtration is that of Somogyi.[4] Otherwise the Folin-Wu technic was followed. The capillary blood sugar was estimated by the method of Lauber and Mattice.[5]

A tourniquet in the ordinary sense of the word was not used, since pressure thus employed produces considerable fluctuations in the venous blood sugar level.[6] Gentle application of the subject's free hand an inch or two above the vein to be needled sufficed for the performance of venipuncture.

The arterial blood was obtained by a prick of the fingertip; a few drops received in a small paraffin cup were enough for the micro-method. It has been found by a number of investigators that this "capillary blood" has the same sugar content as that derived directly from the arteries.[7]

Readings were made on a Klett-Summerson photoelectric colorimeter. Precipitation of the blood was done immediately, since we have found changes of sugar values in some bloods, but not in all, on standing one hour.

* Received for publication May 30, 1949.

The micro-method of Lauber and Mattice, like the Somogyi filtrate in the Folin-Wu procedure, yielded results which checked with yeast fermentation of glucose, and therefore may be regarded as actually representing the true blood sugar without any admixture of nonglucose reducing substances.

There are three accepted types of glucose tolerance tests for the measurement of the adequacy of carbohydrate metabolism. Our object at this time is to make the test more specific for the clinician. Because of this, the intravenous test which is carried out by the injection of 25 gm. of glucose has not been considered. This test has the advantage of determining definitely the capacity of glucose disposal within the body, since the very variable factor of glucose absorption from the small intestine is eliminated. However, the rate of glucose absorption from the intestinal tract has a distinct clinical significance. Furthermore, an intravenous injection of this magnitude has obvious drawbacks in the often impatient applicant for life insurance and in the ambulant subject for office diagnosis.

The second test, the Exton-Rose, two-dose, one hour glucose tolerance test, calls for the taking of 50 gm. of glucose orally and a repetition of this dose in half an hour, the blood sugars being obtained in the fasting state and one-half and one hour after the ingestion of the initial dose of glucose. The advantage of this test is one of speed, in that it requires only one hour for completion. The disadvantage is that only the height of the blood sugar curve is expressed and not the more important two-hour value. The amount of glucose passing into the blood from the small intestine in the two-dose test is probably not greater nor the rate faster than when 100 gm. of glucose are ingested at one time. All of these facts have been discussed in detail by Langner, Romansky and Robin in an article, "The Fallacy of the Exton-Rose Glucose Tolerance Test." [8] The one-hour, two-dose dextrose tolerance test of Exton and Rose, released in 1934,[9] has gone through a period of enthusiastic endorsement, then modification of standards, and, finally, skepticism of its validity, climaxed by the reasoning of Langner et al.

The third glucose tolerance test, in vogue at present, calls for a single dose of glucose given to the fasting individual and the blood sugar determined two hours after the taking of glucose. The objections to the first two tests do not exist here. It is the method of choice of most doctors and laboratories and is the one used in this study. There are still a great many problems concerning the technic of this procedure and its interpretation. Thus far, the fasting state, 12 to 14 hours after the previous night meal, has been generally insisted on and is apparently necessary if the fasting blood sugar is to be significant. The number and timing of the blood sugar estimations vary a great deal. The simplest is the determination of the blood sugar two hours after the test load of glucose has been administered. The fasting blood sugar value is distinctly important and we believe should not be omitted. While many mild or incipient cases of diabetes may have a normal fasting blood sugar, there is no more final test for the diagnosis of

diabetes than an elevated fasting blood sugar. The number and timing of the intervening tests, between the fasting and the two-hour period, are usually planned so that an approach may be had to the maximum blood sugar reading, which usually occurs from 20 to 40 minutes after the taking of glucose. A frequent routine is to obtain the blood sugar one-half hour and one hour after glucose ingestion. This timing has been followed here, making the determinations four: fasting, one-half hour, one hour, and two hours after the taking of glucose. Thus we arrive at an approximate conclusion as to the height and duration of the glucose curve.

When the blood sugars are obtained at 10-minute intervals, it becomes evident that drops and rebounds of distinct significance often occur within the coarser curve of less frequent estimations. Gilbert, Schneider and Bock,[10] determining the blood sugar about every 10 minutes for three hours after glucose ingestion, showed that in 16 of 22 tolerance tests in normal patients, there was, after an early elevation, a rapid drop of blood sugar, often to control levels or less, followed by a subsequent rise. In three of our 50 tolerance curves we have found this to exist (chart 3). A check on the curves of Gilbert et al. reveals that if only the half-hour, one hour and two-hour blood sugars are taken into account, rebound curves are comparatively rare and their incidence is similar to that in our series. Such glucose tolerance tests are obviously within normal limits, even though the blood sugar values at the two-hour interval are high. How this defect in the glucose tolerance test can be eliminated in clinical practice is not clear at the moment.

The diet preceding a glucose tolerance test in nondiabetics has a profound effect on the character of the resulting curve, though a closer scrutiny of the published observations points to a probable exaggeration of this influence. A strictly starch-free diet for a few days (Sweeney[11]), or for a year (Tolstoi[12]), causes an impairment of the glucose tolerance test. A diet containing 20 gm. of carbohydrate (Conn[13]) or even 50 gm. (Himsworth[14]) has the same effect. After a daily starch intake of 125 gm. the subsequent glucose tolerance curve assumes normal proportions (Himworth[14]). Where the crucial figure, between 50 and 125, lies is undetermined. However, it is scarcely conceivable that anyone who eats at all will consume less than 125 gm. of carbohydrate. On the other hand, as stressed by Conn,[13] an emaciated person will have a lowered carbohydrate tolerance. This is hardly a factor with the applicant for life insurance or the ambulant individual, and can be readily eliminated by inspection or brief questioning.

The usual glucose load is 100 gm. This has been followed in our studies. The adjustment of the amount of glucose to the individual's weight is a needless formality, because stout subjects are prone to have an impaired carbohydrate tolerance and because the 100 gm. dose far exceeds the amount necessary for the production of a satisfactory glucose curve. Maclean and de Wesselow[15] showed that 25 gm. of glucose elicit the maximal hyper-

TABLE I

GLUCOSE TOLERANCE TESTS AFTER 100 GMS. GLUCOSE IN 50 AMBULANT NORMAL PERSONS OF VARIOUS AGES

Blood Sugar Mg. per 100 cc.

	Venous Blood								Arterial Blood			
	True Blood Sugar				Folin-Wu Method				Capillary True B.S.			
	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose
Ages 16 to 38 - 20 subjects	83	121	59	40	105	145	73	60	74	135	100	67
	81	95	83	45	98	111	98	62	85	118	142	107
	52	90	70	52	83	125	120	80	82	135	125	91
	86	138	119	65	102	154	139	73	72	128	154	99
	82	105	100	66	114	156	150	111	95	132	140	100
	84	75	61	69	105	86	84	92	65	87	100	103
	86	101	71	70	100	122	88	88	84	114	101	91
	91	105	95	72	105	127	111	95	100	150	144	122
	81	150	130	73	95	168	155	92	77	185	157	92
	90	175	146	77	136	227	205	113	97	200	170	114
	81	135	85	77	100	149	104	95	85	163	92	95
	95	110	89	80	112	135	110	100	127	188	150	144
	85	125	78	80	107	142	105	90	80	145	114	105
	97	125	114	81	104	156	131	100	110	140	155	115
	90	160	137	82	110	191	161	104	90	202	170	110
	88	127	132	83	101	144	144	100	85	129	142	102
	43	108	124	84	113	129	153	106	96	171	193	138
	84	97	109	85	117	132	136	113	97	132	134	120
	80	137	108	92	100	174	156	109	86	143	121	109
	66	116	92	110	91	141	111	136	86	155	112	130
Ages 39 to 59 - 20 subjects	83	83	83	57	96	100	96	76	90	115	86	74
	100	153	148	67	123	221	226	100	86	166	183	92
	75	161	110	73	109	187	154	101	80	149	161	103
	89	121	135	78	100	137	147	92	88	138	150	92
	107	149	110	79	124	178	161	129	121	165	141	101
	83	155	102	80	92	186	139	112	87	177	226	100
	88	134	145	85	111	140	157	92	94	152	154	113
	85	134	100	85	128	178	143	139	81	156	128	78
	89	159	118	86	115	162	139	107	90	165	153	117
	101	183	178	87	136	227	208	123	106	226	229	135
	77	120	90	90	90	134	99	105	77	177	113	125
	87	102	109	90	138	176	178	168	88	132	134	127
	93	156	124	92	130	186	137	120	88	173	200	120
	87	116	168	93	112	143	183	103	96	138	201	125
	97	132	125	94	125	156	148	108	99	142	146	116
	81	152	86	94	106	186	108	130	66	186	180	140
	116	169	137	98	132	179	142	118	121	207	166	133
	80	168	118	107	100	190	142	124	88	195	146	120
	95	150	88	122	109	158	107	137	110	199	135	131
	85	164	107	122	106	192	128	161	71	187	144	129
Ages 61 to 76 - 10 subjects	85	129	86	71	101	145	102	83	82	145	125	99
	67	111	112	72	88	134	133	105	58	135	125	134
	100	131	104	85	131	140	141	117	86	120	126	113
	96	154	166	86	120	209	174	120	75	156	175	100
	87	172	101	87	106	189	137	129	87	181	166	150
	91	95	118	89	112	122	131	117	79	131	150	106
	86	121	93	89	120	153	140	133	86	118	149	93
	93	131	140	94	106	181	167	123	93	187	200	137
	86	105	126	103	100	135	146	127	85	122	126	113
	91	162	154	109	108	188	178	132	91	194	208	163

glycemia, and that a larger amount tends to prolong the period during which the blood sugar remains elevated, rather than to increase the actual height of the curve. After the ingestion of 25 gm. of glucose, the blood sugar returns to a normal level in 90 minutes; with 50 or 100 gm., in two hours. The pros and cons for these various doses make this, to a certain extent, an open question to be solved only by long and tedious investigations. The usual amount of glucose in this country is 100 gm.; in England some authorities (Lawrence [16]) give 50 gm. We have used 100 gm. because this adheres most closely to current practice and fulfills all possible requirements of the glucose tolerance test.

The complete results of our tests are given in table 1. An analysis of the various details concerned in the interpretation of these glucose tolerance curves is furnished in the subsequent tables and charts.

Old Age—Rest

It is apparent on inspection of table 1 that sugar tolerance in the old age group did not differ from that in younger persons. This may be gathered most readily from a study of the true venous blood sugar figures, which we believe furnish the most reliable criteria. Spence in 1920 and others since then [17] have found impaired glucose tolerance in the aged. Short and Johnson [18] (1938), checking ambulant persons, failed to demonstrate any noticeable change in the sugar tolerance that could be ascribed to age. No attention was given to their publication. Blotner,[2] in 1945, showed that bed rest resulted in abnormal blood sugar curves and that hospitalized individuals yielded unsatisfactory results. Marble,[19] one year later, expressed the opinion, based on Blotner's findings, that "at least part of the decreased sugar tolerance found in elderly persons may be due to relative inactivity." From our results, especially in view of the report of Short and Johnson, it may be claimed that old age does not change the character of the glucose tolerance curve from that found in young individuals.

The subjects for tests in the aged have usually been inmates of homes for old people, or hospitalized subjects. Patients at rest have yielded the impression that almost any disease—arthritis, carcinoma, lues, hypertension, nephritis, and many others—have a diminished carbohydrate tolerance. It is evident that this whole matter merits a thorough revision on ambulant and not on resting or bedridden individuals. The beneficial effect of exercise in diabetes is well known, and we have an indication here that complete lack of physical effort may be the first step towards diabetes.

Greater stores of glycogen and phosphate esters are found in the muscles of animals which have been trained to perform prolonged work.[20] This observation furnishes a reason for the type of glucose tolerance characteristic of persons who are confined to bed and inactive. Furthermore, it suggests the possibility that blood sugar responses to ingested glucose may not be normal in animals postoperatively or even when confined to cages.

Nonglucose Reducing Substances

The most favored blood sugar method is the Folin-Wu procedure, which includes a considerable amount of nonfermentable reducing substances which are not glucose. The difference between estimations obtained by the Folin-Wu technic and that for true blood sugar lies in the nonglucose reducing substances. These materials have been regarded as amounting to between 10 and 30 mg. per 100 c.c. of blood, and as a fairly constant source of error that could be satisfactorily balanced by a set arbitrary adjustment.

Table II

NONGLUCOSE REDUCING SUBSTANCES (VENOUS BLOOD) IN SUGAR TOLERANCE TESTS AFTER 100 GMS. GLUCOSE IN 50 AMBULANT NORMAL PERSONS OF VARIOUS AGES

Nonglucose Reducing Substances Mg. per 100 cc.				
Ages 16 to 38 - 23 Subjects	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose
	22	24	14	20
	17	16	15	17
	31	35	50	28
	16	16	20	8
	32	51	50	45
	21	11	23	23
	14	21	17	18
	14	22	16	23
	14	18	25	18
	46	52	59	58
	19	14	19	17
	17	25	21	20
	22	17	27	10
	7	31	17	19
	20	31	24	22
	13	17	12	17
	20	21	29	22
	33	35	27	28
	20	37	48	17
	25	25	19	26
Ages 39 to 59 - 20 Subjects	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose
	13	17	13	19
	23	66	78	33
	34	26	44	28
	11	16	12	14
	17	29	51	50
	9	31	37	32
	23	6	12	7
	43	64	43	54
	26	3	21	21
	35	64	30	36
	13	14	9	15
	51	74	69	78
	37	30	13	28
	25	27	15	10
	28	24	23	14
	25	34	22	36
	16	10	5	20
	20	22	24	17
	14	8	19	15
	21	28	21	39
Ages 61 to 76 - 10 Subjects	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose
	16	16	16	12
	11	23	21	33
	31	9	37	28
	24	55	8	34
	19	17	36	42
	21	27	13	28
	34	32	47	44
	13	50	27	29
	14	30	20	24
	17	26	24	23

Nonglucose reducing substances are the materials determined as sugar by some methods (in this presentation Folin Wu) which are not included in the values for blood sugar as estimated by fermentation or other procedures which yield "true blood sugar" levels. The unpredictable and often marked variation of the nonglucose reducing substances is evident. These figures are derived from results given in Table 1.

A review of the literature shows that the facts are somewhat at variance with the generally accepted conclusions. Nonglucose reducing substances as high as 35 mg.,[21] 40 mg.,[22] and even higher were reported for normal persons. In cases of advanced nephritis and of arteriosclerosis with renal insufficiency, Hiller, Linder and Van Slyke [21] found the nonglucose reducing substances frequently above 40 mg. and as high as 70 mg. per 100 c.c. of blood, which they believed accounted for the diminished glucose tolerance considered characteristic of those diseases. Somogyi [23] discovered that the

nonglucose reducing substances were very unevenly distributed between the plasma and the red blood corpuscles. According to his determinations, the nonglucose reducing substances averaged 27 mg. per 100 c.c. in whole blood, 10 mg. in the plasma, and 47 mg. in the blood corpuscles. This finding makes it clear that in whole blood determinations carried out by the Folin-Wu method the corpuscular volume plays a big rôle.

TABLE III

NONGLUCOSE REDUCING SUBSTANCES ABOVE 30 MG. PER 100 CC. OF BLOOD IN 50 CONSECUTIVE GLUCOSE TOLERANCE TESTS IN NORMAL SUBJECTS

	FASTING		AFTER INGESTION 100 GMS. GLUCOSE					
			1/2 HOUR		1 HOUR		2 HOURS	
	No. Cases	Mg. per 100 cc.	No. Cases	Mg. per 100 cc.	No. Cases	Mg. per 100 cc.	No. Cases	Mg. per 100 cc.
20 subjects	4	31	7	31	4	48	2	45
		32		31		50		58
ages 16- 38		33		35		50		
		46		35		59		
				37				
				51				
				52				
20 subjects	5	34	6	31	6	37	8	32
		35		34		43		33
ages 39- 59		37		44		44		36
		43		44		51		36
		51		68		69		39
				74		78		50
								54
								78
10 subjects	2	31	3	32	3	36	4	33
		34		50		37		34
ages 61- 76				55		47		42
								44
TOTAL	11		16		13		14	

NUMBER OF CASES WITH NONGLUCOSE REDUCING SUBSTANCES ABOVE 30 MG. PER 100 CC. BLOOD

In 1 only of the 4 determinations	6
In 2 only of the 4 "	8
In 3 only of the 4 "	4
In 4 of the determinations	5

Total number of instances in which nonglucose reducing substances exceeded 30 mg. per 100 cc. of blood 54

Percentage of the nonglucose reducing substances exceeding 30 mg. per 100 cc. in the 200 blood sugar determinations ... 27%

In the present series, many of the determinations of nonglucose reducing substances yielded values above 30 mg. per 100 c.c. of blood, being as high as 78 (table 2). A closer analysis of these figures, as given in table 3, shows that there is no predominance of the values above 30 mg. per 100 c.c. of blood of the nonglucose reducing substances in any age group, nor at a given time after the ingestion of glucose. The high figures were found in 23 of the 50 subjects, 14 having one or two determinations above 30, four having three, and five having four determinations of nonglucose reducing substances above 30 mg. per 100 c.c. of blood. In 54 instances of the 200 blood sugar deter-

minations (that is, 27 per cent), the values for nonglucose reducing substances exceeded 30 mg. In some instances the nonglucose reducing substances did remain constant, as shown in the lower four curves on chart 1. This applies to about half the normal persons examined. In the other half, at least one determination exceeded the upper normal limit of 30 mg. per 100 c.c. of blood, and the values for the nonglucose reducing substances were extremely irregular and unpredictable, as shown in the six upper curves of chart 1.

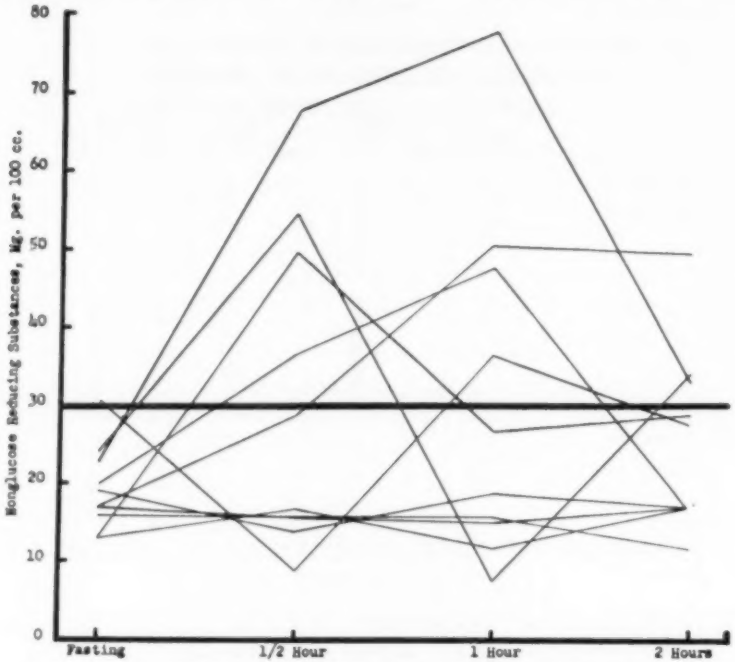


CHART I. Nonglucose reducing substances (difference between true blood sugar and Folin-Wu methods) in normal glucose tolerance tests. Only 10 of the 50 tests are charted: six which exhibited the greatest variation in the nonglucose reducing substances and four which exhibited the lowest. A charting of all the nonglucose substances was attempted but with 50 curves the chart was not clear. In 27 of the glucose tolerance curves (54%) the nonglucose reducing substances did not exceed 30 mg. per 100 c.c. of blood; these yielded curves corresponding to the four lower flat curves. In 23 of the curves (46%) at least one determination exceeded the accepted upper normal limit of 30 mg. per 100 c.c. of blood confusing the interpretation of glucose levels as shown in the upper six curves.

These findings confirm our earlier reports,[1] which concerned themselves largely with cases of diabetes. It is evident that the Folin-Wu test will often yield inaccurate results which are obviated by the use of a true blood sugar method. This matter will be taken up in detail when deviations from the normal standards are discussed (see table 6).

Arteriovenous Blood Sugar Difference

Arteriovenous blood sugar difference, that is, the divergence between the "true" blood sugar as determined in the venous blood and that in the arterial blood, is given in table 4 and depicted graphically in chart 2. The arteriovenous blood sugar difference in the fasting state is approximately at the zero level. There is universal agreement on this point. The amount of arteriovenous blood sugar difference after the taking of glucose has been reported as varying greatly, and that has been our finding (chart 2). The highest value at the one hour mark in the present series was 124 mg. per 100 c.c.

Table IV

Arteriovenous Blood Sugar Differences in Sugar Tolerance Tests after 100 Gms. Glucose in 50 Ambulant Normal Persons of Various Ages Obtained by the True Venous Blood Sugar and True Arterial (Capillary) Blood Sugar Methods

Arteriovenous Blood Sugar Difference Mg. per 100 cc.

Ages 16 to 38 - 20 Subjects					Ages 39 to 59 - 20 Subjects				Ages 61 to 76 - 10 Subjects			
	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose	Fasting	½ Hr. after Glucose	1 Hr. after Glucose	2 Hrs. after Glucose
	- 9	+14	+41	+27	+ 7	+32	+ 3	+17	- 3	+16	+39	+28
	+ 4	+53	+59	+62	-14	+13	+35	+25	- 9	+24	+13	+62
	+30	+45	+55	+39	+ 5	-12	+54	+30	-14	-11	+22	+28
	-14	-10	+35	+34	- 1	+17	+15	+14	-21	+ 2	+ 9	+14
	+13	+27	+40	+34	+14	+16	+51	+50	0	+ 9	+65	+63
	-19	+12	+39	+34	+ 4	+22	+124	+20	-12	+36	+32	+17
	- 2	+13	+30	+21	+ 6	+18	+ 9	+28	0	- 3	+56	+ 4
	+ 9	+45	+49	+50	- 4	+22	+28	- 7	0	+56	+60	+43
	- 4	+35	+27	+19	+ 1	+ 6	+35	+31	- 1	+17	0	+10
	+ 7	+25	+24	+26	+ 3	+43	+51	+45	0	+32	+54	+54
	+ 4	+28	+ 7	+18	0	+57	+23	+35				
	+32	+78	+61	+64	+ 1	+30	+25	+37				
	- 5	+20	+26	+25	- 5	+17	+76	+28				
	+13	+15	+41	+34	+ 9	+22	+33	+32				
	0	+42	+33	+28	+ 2	+10	+21	+22				
	- 3	+ 2	+10	+19	-15	+34	+94	+46				
	+ 3	+63	+69	+54	+ 5	+18	+29	+20				
	+13	+35	+25	+28	+ 8	+27	+28	+13				
	+ 6	+ 6	+13	+17	+15	+49	+47	+ 9				
	+20	+39	+20	+20	-14	+23	+37	+ 7				

of blood, whereas the lowest was zero. There was no outstanding difference according to age (table 4).

From our results it would appear that the arterial blood furnishes more accurate information on the amount of sugar absorbed from the intestine than does the venous blood. It occurs quite commonly that when the venous blood sugar curve is flat, the arterial blood sugar curve is distinctly elevated. The measure of glucose absorption from the intestine is therefore more accurately indicated by the arterial than by the venous blood sugar curves, although the possibility that the liver takes up the glucose passing

through it in the portal vein must be considered as a factor that might prevent an elevation of arterial blood sugar. Consequently, while a rise in the arterial blood sugar is a more reliable indicator of glucose absorption than is the venous blood sugar, it is conceivable that even the arterial blood may fail to reflect glucose absorption from the intestine.

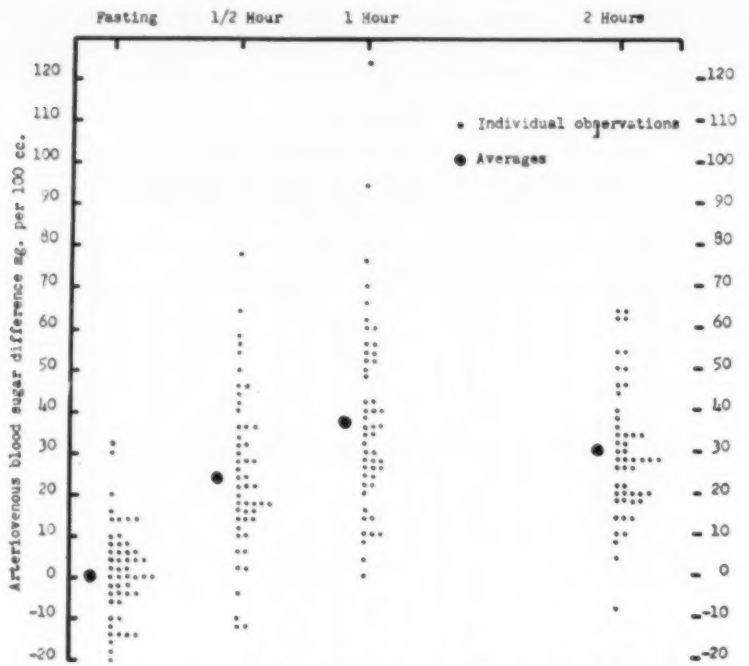


CHART II. Arteriovenous blood sugar difference after 100 gm. glucose in 50 normal individuals. The rise of the arteriovenous blood sugar difference after glucose ingestion is evident. Especially noteworthy is its persistence at the two-hour period when in most instances the venous blood sugar has returned to the fasting level.

According to our calculations, 1 mg. of arteriovenous blood sugar difference indicates the disposition of about 1 gm. of glucose per hour in the muscles and skin:

Blood flow per minute through extremities in man at rest	1,800 c.c.[34]
Arteriovenous blood sugar difference of 1 mg. per 100 c.c. indicates that the peripheral tissues (muscle and skin):	
absorb in one minute (1,800 by $\frac{1}{100}$ = 18 mg.)	18 mg.
absorb in one hour (18 by 60 = 1,080 mg., or 1 gm.)	1 gm.

In the two-hour period of the glucose tolerance test the average arteriovenous difference is about 30 mg. per 100 c.c. of blood, somewhat higher at the one-hour interval and lower at the one-half hour (chart 2). The deviations from the average are very great, which shows that the assimilation of glucose by the peripheral tissues is far from constant, though it usually involves a considerable amount of glucose. If the figure 30 is regarded as the approximate average arteriovenous blood sugar difference existing throughout the two hours, and if our calculations that 1 mg. difference indicates an assimilation of 1 gm. per hour, then in two hours the peripheral tissues would be taking up 60 gm. of glucose. These are conservative estimates, especially as the subjects were far from being at rest in the physiologic sense and the flow of blood circulating through the extremities was in all probability much greater than the amount stated.

It has been shown by Carpenter and Fox [25] that there is glucose combustion at the rate of about 10 gm. per hour after 100 gm. of glucose are ingested. Considering the fact that hyperglycemia checks the formation of glucose by the liver, there would be in the average normal individual 80 gm. of glucose (20 gm. by combustion, 60 gm. taken up by the peripheral tissues) disposed of by extrahepatic agencies within the two hours' duration of the glucose tolerance test. The contention of Soskin et al.[26] that the liver takes care of all the ingested glucose is distinctly negated by these findings. In fact, the majority of cases (table 4 and chart 2) show a marked arteriovenous difference, indicating that extensive assimilation of ingested glucose by the peripheral tissues is a normal process. Two of the tolerance tests from table 1 are given in detail. They demonstrate the extremes in variation that may occur in the arteriovenous blood sugar difference and how the peripheral tissues may or may not be active in the assimilation of glucose.

Example of maximal utilization of glucose by the peripheral tissues which to a certain degree exists in nearly all normals and in a very mild diabetes:

	Blood Sugar mg. per 100 c.c.			
	Fasting	After Glucose Ingestion		
		½ Hour	1 Hour	2 Hours
True Venous B.S.	93	131	140	94
True Arterial B.S.	93	187	200	137
A-V Difference	0	56	60	43

Example of poor utilization of glucose by peripheral tissues in a normal person, probably disposal of glucose in the liver (this is the exception in normals). From the rise in both the venous and the arterial blood sugar it is certain that glucose has been absorbed from the intestine.

	Blood Sugar mg. per 100 c.c.			
	Fasting	After Glucose Ingestion		
		½ Hour	1 Hour	2 Hours
True Venous B.S.	96	154	166	86
True Arterial B.S.	75	156	175	100
A-V Difference	−21	2	9	14

The assimilation of glucose by the peripheral tissues, as registered by the arteriovenous blood sugar difference, especially two hours after the ingestion of glucose, makes it clear that the venous blood sugar measures the tolerance to glucose more accurately than does the arterial. The absorption of glucose from the small intestine is more satisfactorily recorded by the arterial blood sugar than by the venous blood. The constant and marked arteriovenous blood sugar difference after the ingestion of glucose makes it certain that in most normal people the peripheral tissues are of greater importance than the liver in the assimilation of glucose, though in some instances the latter may play a significant rôle.

Standards for Normal Glucose Tolerance Tests

The criteria by which glucose tolerance tests are judged vary according to the blood sugar method used. The generally accepted figures for the venous blood determined by the Folin-Wu method and often arbitrarily applied to the other blood sugar methods are: 120 mg. per cent or less for fasting, a high blood sugar of 170 or less after the administration of glucose, and in two hours after glucose, 120 or less (see table 5). For the arterial blood sugar, the standards have not been so precisely set forth. The figures advocated by Lawrence,[16] and apparently in vogue in England, are 120 mg. per cent or less for fasting, 200 as the high point, and 120 or less at the two-hour period. It is necessary to realize that these figures are given for a test load of 50 gm. of glucose and not the 100 gm. usual in America. This, as previously discussed, would not modify the fasting blood sugar or the height of the curve but would tend to lower the two-hour value nearer the normal mentioned than has been our experience (see table 1). From the data given in table 1, we believe that the criteria for true blood sugar in venous blood are: 100 mg. per cent or less on fasting, a limit of 150 for the height of the curve, and 100 or less for the two-hour period. These values are 20 mg. less than those given for the Folin-Wu determinations, which is in conformity with prevailing practice but not arrived at by simple adoption but by the actual observations we carried out. The criteria for glucose tolerance tests are summarized in table 5.

The deviations from the normal standards for glucose tolerance tests in the 50 normal persons observed by us are given in table 6.

TABLE V

CRITERIA FOR GLUCOSE TOLERANCE TESTS

BLOOD AND TESTS	BLOOD SUGAR MG. PER 100 CC.		
	FASTING	HIGH	2 HOUR
Venous blood Generally accepted for all B.S. methods usually Folin-Wu	120 or less	170 or less	120 or less
Venous blood True B.S. methods advocated in this presentation	100 or less	150 or less	100 or less
Arterial blood Generally accepted Methods not specified	120 or less	200 or less	120 or less

THE FASTING BLOOD SUGAR

This is at a normal level in practically every nondiabetic. It is a test for fairly severe diabetes, since mild diabetics and those of recent onset have a fasting blood sugar that is within normal limits. In the fasting true venous blood sugar determinations, three were above the normal of 100: 107, 101, and 116; in none of these was the two-hour figure elevated, so that there was no complete evidence of diminished carbohydrate tolerance; two of the high fasting blood sugars—107 and 101— deviated so slightly from the standard that they have no significance; the third, 116, was definitely high. Hence, the fasting true venous blood sugar is not an absolute criterion of the existence of diabetes, but a 2 per cent possibility exists that the fasting blood sugar is greater than it should be in normal individuals. However, this error appears to be eliminated when the full two-hour curve is considered.

TABLE VI

DEVIATIONS FROM THE NORMAL STANDARDS (SEE TABLE 5)

FOR GLUCOSE TOLERANCE TESTS IN 50 NORMAL PERSONS

	VENOUS BLOOD SUGAR				ARTERIAL (Capillary) BLOOD SUGAR	
	TRUE (Number)	Percent	FOLIN-WU (Number)	Percent	(Number)	Percent
Fasting	(3)	6	(10)	20	(3)	6
High	(16)	32	(20)	40	(6)	12
Two-Hour	(6)	12	(14)	28	(16)	32
Fasting and Two-hour	(0)	0	(3)	6	(0)	0
High and Two-hour	(3)	6	(11)	22	(10)	20
Fasting, High and Two-hour	(0)	0	(3)	6	(2)	4

The height of the blood sugar curve evidently deviates so frequently from the normal standards as not to be of great importance in evaluating glucose tolerance tests. Excluding the height of the blood sugar, the true venous blood sugar furnishes decidedly more reliable data than the Folin-Wu test and, as might be expected from the arterio-venous difference (Chart 2) than the arterial blood estimations, especially at two hours after the taking of glucose.

The fasting arterial true blood sugar yielded about the same results as the true venous blood sugar estimations. Three determinations were higher than the standard of 120: 121, 121, and 127. All of these are within limits of error in the estimations. The upper level of 120 for the fasting blood sugar in the arterial blood therefore seems fairly correct, as does the value of 100 for the true venous blood sugar.

The result for the fasting venous blood sugar as revealed by the Folin-Wu method is much less satisfactory. In 10 instances they were higher than the normal standard of 120, varying from 123 to 138. Four of these were less than 10 mg. too high; six were 10 mg. or more above the normal standard of 120. In all of the latter the nonglucose reducing substances exceeded 30 mg. per 100 c.c. of blood, showing that the cause of the abnormality could be ascribed to the nonspecificity of the Folin-Wu technic.

Allowing for a maximal 9 mg. error in carrying out blood sugar determinations, the final results for abnormal figures in the fasting blood sugar are: 2 per cent in true venous blood sugar, 0 in the arterial blood sugar, and 12 per cent in venous blood sugar determined by the Folin-Wu procedure.

Height Of The Blood Sugar

Height of the blood sugar in itself has not been regarded as a sign of an impaired glucose tolerance. In nondiabetics it depends upon the rapidity of absorption from the intestinal tract,[8] becoming extreme when the so-called "dumping syndrome" supervenes following gastroenterostomy or subtotal gastrectomy.[27] The immoderate elevation of the blood sugar in these cases returns to normal within two hours after glucose ingestion. Thus, these curves are high but not prolonged. A high, prolonged curve is characteristic of a diminished carbohydrate tolerance. Maclean,[28] as long ago as 1922, found that the upper value of the blood sugar in a sugar tolerance test was not diagnostic of diabetes. He termed these curves "lag curves," because of the apparent delay in sugar utilization. On the other hand, Marble[29] believes that the height to which the curve goes cannot be disregarded, and that a diagnosis of diabetes is not justified unless the blood sugar level reaches 170. Our experience in a follow-up series failed to show diabetes in high curves without other abnormality. The height of the blood sugar curve deviates so frequently from the normal (32 per cent for true venous blood and 40 per cent of the cases according to the Folin-Wu method) that in itself it cannot be regarded as a reliable means of interpreting glucose tolerance tests. However, when combined with the drop in blood sugar judged by the two-hour level, it is a necessary element for the diagnosis of diabetes.

Blood Sugar Two Hours After Glucose Ingestion

This is regarded by most observers as the key figure of the data furnished by the glucose tolerance curve. It has become evident that the two-hour

blood sugar must be elevated if the test is to be considered as indicating a diminished ability to utilize carbohydrate. A survey of the two-hour results (table 6) shows that of the true venous blood sugar, six, or 12 per cent exceeded the normal level, of the Folin-Wu method 14, or 28 per cent, and of the arterial blood 16, or 32 per cent. The lack of accuracy of the arterial blood and of the Folin-Wu method in venous blood is very great and can be easily explained by the large arteriovenous difference and by the presence of unexpected amounts of nonglucose reducing substance, neither of which can be avoided.

The deviation in six instances of the true venous blood sugar at the two-hour period shows that three of them, varying from 103 to 109 mg., 9 mg. or less out of line, and consequently were of negligible significance. The other three were 110, 122, and 122 mg. per 100 c.c. of blood. In each of these

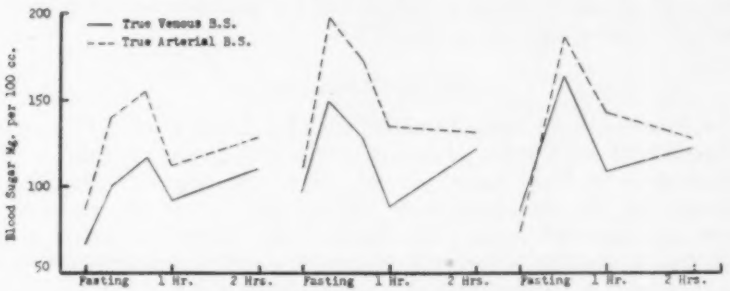


CHART III. "Rebound" blood sugar curves. These are 3 curves of the 6 which have an abnormally high true venous blood sugar 2 hours after the ingestion of glucose. In 2 of these the true venous blood sugar is less than 100 mg. per 100 c.c. at the one hour level and in the third almost reaches this value. These are obviously normal blood sugar curves in spite of the high 2 hour readings. There appears to be no easy way to obviate this possible error; a repetition of the blood sugar curve with frequent blood sugar determinations, every 5 to 10 minutes, would seem to be the only solution.

three the true venous blood sugar at the one-hour interval was lower than the two-hour value, the actual low at the end of one hour being 88, 92, and 107 mg. Consequently, these curves were in reality normal, even though the two-hour glucose was high, because a preceding blood sugar after glucose ingestion had been within normal or practically normal limits. These three rebound curves are given in chart 3. As mentioned before, this is of common occurrence in glucose tolerance curves if the blood sugar is estimated at five minute intervals.[10] There appears to be no way of obviating this 6 per cent error in the glucose tolerance test except by repetition of the procedure with more frequent determinations of the blood sugar, especially before and after the one-hour interval. If the rebound curves are properly interpreted, even with the present figures we would have an almost perfect score for the two-hour blood sugar determinations in the true venous blood sugar.

High And Two-Hour Blood Sugar

It is generally believed that every diabetic exhibits a high and prolonged blood sugar curve but that not every high, prolonged blood sugar curve is pathognomonic of diabetes. The present investigation shows that for the Folin-Wu method, 22 per cent of normals, and for the arterial blood sugar, 20 per cent of normals, have a high prolonged blood sugar curve, whereas only 6 per cent show this for the true venous blood sugar. Of these three cases, constituting a 6 per cent error, there were two blood sugars at the two-hour period of 107 and 109, which is a questionable divergence from the normal. The third had a two-hour blood sugar of 122 but was one of the rebound blood sugar curves, the one-hour figure being 107. Consequently, even these three in the true venous blood sugar determinations would be classified among the doubtful positives, giving almost a faultless result for the true venous blood sugar method in interpreting the glucose tolerance curves on the basis of being high and prolonged.

Renal Glycosuria

A lowering of the "renal threshold" to blood glucose results in a harmless elimination of sugar in the urine and is known as a renal glycosuria. The concentration of blood sugar necessary to produce sugar in the urine of normals has been considered to be 170 mg. per 100 c.c. of venous blood sugar, as determined by the Folin-Wu method. The error inherent in this procedure because of the inclusion of variable amounts of nonglucose reducing substances has been discussed. Furthermore, it is a serious misconception to regard the venous blood sugar level as the determining factor for the amount of glucose that is filtered through the glomeruli. The glucose concentration in the plasma of the arterial blood is obviously the crucial point. Several investigators have stressed this, but clinicians have not, as a rule, taken it into account. While the urinary findings are not charted in this article, we did carry them out, and found that the level for arterial blood sugar at which glucose is prone to appear in the urine is about 200 mg. per cent. The arterial blood sugar is closer to that in the arterial plasma than it is to the blood sugar in the venous blood. Arterial blood plasma sugar is supposed to be somewhat higher than arterial blood sugar. Whether a revision of glucose tolerance tests on the basis of determining plasma blood sugars in venous and arterial bloods will yield more satisfactory results remains to be checked.

The idea is widespread that the "renal threshold" to glucose is lower when the blood sugar is on the downstroke of the curve than when it is rising. Where this conception originated we do not know, but one of us, in a publication in 1925, stated that it was well known. When the "renal threshold" to glucose is measured by the true arterial blood sugar, it is evident that the arterial blood sugar at certain periods in the blood sugar

curve will rise while the venous blood sugar falls (chart 4). Although this is evident only in some of the curves presented, it would, without doubt, be demonstrated in nearly all of them if the blood sugars had been carried out at five minute instead of half-hour intervals. From these findings we believe that the "renal threshold" to glucose should be determined by the arterial blood sugar, and that when this is done the blood level resulting in glycosuria will not become lowered when the venous blood sugar diminishes after reaching its peak.

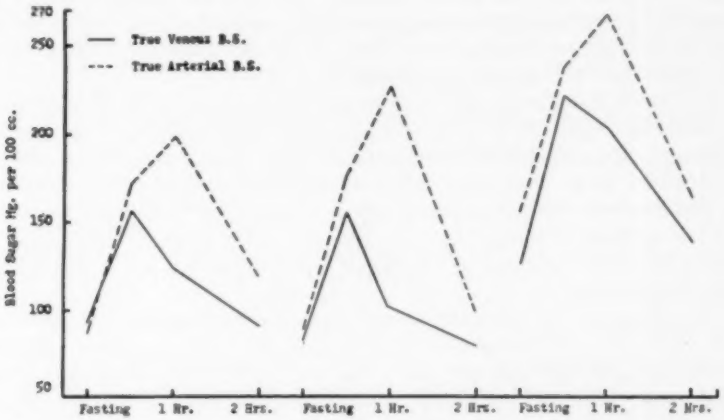


CHART IV. Divergent trends of arterial and venous blood sugars determination of the renal threshold to glucose. The first two curves are from this series of normals, the third curve on the right is from a probable diabetic patient. The above three blood sugar curves make it apparent that there may be serious errors in estimating the "renal threshold" to glucose if it is judged by the venous blood sugar. These curves would cancel the idea that the "renal threshold" to glucose is lower when the venous blood sugar is diminishing than when it is rising, because the arterial blood sugar level which determines the amount of glucose filtered by the glomeruli rises from the half to one-hour period while the venous blood sugar is lower.

SUMMARY AND CONCLUSIONS

A study of glucose tolerance tests on venous and arterial blood in normal, ambulant persons of various ages is presented.

The one dose, two-hour glucose tolerance test was selected as the best method available for the clinician to determine the existence of diabetes mellitus.

Two procedures were used to estimate the sugar in venous blood: the generally accepted Folin-Wu method, and one that yielded true blood sugar levels. The resort to a minimal degree of localized pressure, instead of the customary encircling high compression tourniquet, added to the accuracy of our results.

The fingertip (arterial or capillary) blood sugar was determined according to true blood sugar values.

In the aged there was no impairment of glucose tolerance. This is contrary to accepted beliefs, which have been based largely on hospitalized individuals. Blotner has shown that bed rest interferes with blood sugar curves, and our observations solely on ambulant persons confirm this. It is probable that a diminished carbohydrate tolerance, accredited to arthritis and other diseases, may be similarly explained.

The frequently great (as high as 78 mg. per cent), very variable and unpredictable amounts of nonglucose reducing substances included as glucose by the Folin-Wu method make it obvious that serious analytic errors may be avoided by resorting to a true blood sugar method. The one suggested here requires the same steps as the Folin-Wu technic, the only change being the substitution of Somogyi's precipitant.

The marked and inconstant arteriovenous blood sugar difference developing after the ingestion of glucose makes the interpretation of the glucose tolerance curves based on the arterial blood sugar, less accurate, especially at the two-hour point, than those based on venous blood sugar determinations.

The presence of marked arteriovenous blood sugar differences indicates that the peripheral tissues (muscle and skin) are active in disposing of glucose and that the removal of glucose from the blood is not carried out solely by the liver.

Determinations of true venous blood sugar furnish the most dependable data from which to construct glucose tolerance curves. The deviation from the normal is much less frequent and of lesser degree than when the venous blood sugar measured according to the Folin-Wu method is employed, or when the arterial blood sugar levels are used.

The renal threshold to glucose should, obviously, be read with the arterial and not the venous blood sugar as a guide. The prevalent idea that the renal threshold to glucose is lower on the downstroke of the glucose tolerance curve than on the upstroke, based on venous blood sugar levels, is probably incorrect, because the arterial blood sugar often rises from the half to the one hour mark, while the venous blood sugar falls during this period. The renal threshold to glucose as measured by the true arterial blood sugar was found to be fairly constant at 200 mg. per cent.

The absorption of glucose from the small intestine is more accurately recorded by the arterial blood sugar than by the venous blood sugar.

Most of the errors commonly encountered in the glucose tolerance tests in normals may be avoided by the use of true blood sugar determinations on venous blood in ambulant individuals. The criteria for normality with this method are 100 mg. or less of glucose per 100 c.c. of blood in the fasting state; a maximum height of the curve of 150 mg. or less; and two hours after the ingestion of 100 grams of glucose, a level of 100 mg. or less. A diminished carbohydrate tolerance is indicated when both the height of the blood sugar curve and the two-hour values are elevated. The occasional occurrence of high prolonged curves in normal persons can be accounted for, in

the present series at least, by the development of rebound curves—that is the lowering of the blood sugar to approximately fasting levels at about the one-hour period with a recoil to higher values at two hours. In doubtful cases, the only certain way to avoid this error is to carry out the blood sugar determinations more frequently between the one to the two-hour point.

BIBLIOGRAPHY

1. (a) Mosenthal, H. O., and Barry, E.: Evaluation of blood sugar tests, Am. J. Digest. Dis. **13**: 160–170, 1946.
   (b) Mosenthal, H. O.: Interpretation of glucose tolerance tests, M. Clin. North America **31**: 299–312, (March) 1947.
2. Blotner, H.: Effect of prolonged physical inactivity on tolerance of sugar, Arch. Int. Med. **75**: 39–44, 1945.
3. Folin, O., and Wu, H.: A system of blood analysis, a simplified and improved method for determination of sugar, J. Biol. Chem. **41**: 367, 1920.
4. Somogyi, M.: A method for the preparation of blood filtrates for the determination of sugar, J. Biol. Chem. **86**: 655, 1930.
5. Lauber, F. U., and Mattice, M. R.: Microdetermination of blood glucose, J. Lab. and Clin. Med. **29**: 113–116, 1944.
6. Loughlin, W. C., Mosenthal, H. O., and Halpern, R.: Effect of tourniquets on venous blood sugar values, J. Lab. and Clin. Med. **28**: 1165–1167, 1943.
7. (a) Foster, G. L.: Studies on carbohydrate metabolism. 1. Some comparisons of blood sugar concentrations in venous blood and in finger blood, J. Biol. Chem. **55**: 291–301, 1923.
   (b) Jonas, L.: A note on cutaneous venous blood sugar difference in normal males and females and in thyroid disease, J. Clin. Investigation **12**: 139–141, 1933.
   (c) Langner, P. F., Jr., and Fies, H. L.: Blood sugar values of blood obtained simultaneously from radial artery, antecubital vein and finger, Am. J. Clin. Path. **12**: 559–562, 1942.
8. Langner, P. H., Jr., Romansky, M. J., and Robin, E. D.: The fallacy of the Exton-Rose glucose tolerance test, Am. J. M. Sc. **212**: 466–470, 1946.
9. Exton, W. G., and Rose, A. R.: The one-hour, two-dose dextrose tolerance test, Am. J. Clin. Path. **4**: 381–399, 1934.
10. Gilbert, M., Schneider, H., and Bock, J. C.: Blood sugar studies, J. Biol. Chem. **67**: 629–645, 1926.
11. Sweeney, J. S.: Dietary factors that influence the dextrose tolerance test, Arch. Int. Med. **40**: 818–830, 1927.
12. Tolstoi, E.: Effect of an exclusive meat diet lasting one year on the carbohydrate tolerance of two normal men, J. Biol. Chem. **83**: 747–758, 1929.
13. Conn, J. W.: Interpretation of the glucose tolerance test. The necessity of a standard preparatory diet, Am. J. M. Sc. **199**: 555–564, 1940.
14. Himsworth, H. P.: The influence of diet on the sugar tolerance of healthy men and its reference to certain extrinsic factors, Clin. Sc. **2**: 67–94, 1935.
15. Maclean, H., and de Wesselow, O. L. V.: The estimation of sugar tolerance, Quart. J. Med. **14**: 103–119, 1921.
16. Lawrence, R. D.: Symptomless glycosurias; differentiation by sugar tolerance test, M. Clin. North America **31**: 289–297, (March) 1947.
17. (a) Spense, J. C.: Some observations on sugar tolerance with special reference to variations found at different ages, Quart. J. Med. **14**: 314–326, 1921.
   (b) Hale-White, R., and Payne, W. W.: Dextrose tolerance curve in health, Quart. J. Med. **19**: 393–410, 1926.

(c) Marshall, F. W.: Sugar content of the blood in elderly people, Quart. J. Med. **24**: 257–284, 1931.

(d) Deren, M. D.: Dextrose tolerance in the aged, J. Lab. and Clin. Med. **22**: 1138–1141, 1937.

18. Short, J. J., and Johnson, H. J.: Glucose tolerance in relation to weight and age; forty-ninth annual meeting of the Association of Life Insurance Medical Directors of America, October, 1938.
19. Marble, A.: The treatment of diabetes mellitus, Joslin et al., 8th ed., Philadelphia, Lea & Febiger, 1946, p. 166.
20. Palladin, A., quoted by Soskin, S., and Levine, R.: Carbohydrate metabolism, Chicago, University of Chicago Press, 1946, page 14.
21. Hiller, A., Linder, G. C., and Van Slyke, D. D.: The reducing substances of the blood, J. Biol. Chem. **64**: 625–638, 1925.
22. Folin, O.: The determination of sugar in blood and in normal urine, J. Biol. Chem. **67**: 357–370, 1926.
23. Somogyi, M.: Reducing non-sugars and true sugar in human blood, J. Biol. Chem. **75**: 33–43, 1927.
24. Richards, D. W., Jr.: Observations on the dynamics of the systemic circulation in men, Bull. New York Acad. Med. **22**: 630–646, 1946.
25. Carpenter, T. M., and Fox, E. L.: Gaseous exchange of the human subject II as affected by small quantities of dextrose, J. Nutrition **2**: 375–388, 1930.
26. Soskin, S., Essex, H. E., Herrick, J. F., and Mann, F. C.: Mechanism of regulation of the blood sugar by the liver, Am. J. Physiol. **124**: 558–567, 1938.
27. Zollinger, R. M., and Hoerr, S. O.: Gastric operations—troublesome post-operative symptoms with special reference to carbohydrate ingestion, J. A. M. A. **134**: 575–579, 1947.
28. Maclean, H.: Modern methods in diagnosis and treatment of glycosuria and diabetes, London, Lea & Febiger, 1922, page 42.
29. Marble, A.: The treatment of diabetes mellitus, Joslin et al., 8th ed., Philadelphia, Lea & Febiger, 1946, pp. 160–161.

THE ASSOCIATION OF LAENNEC'S CIRRHOSIS WITH DIABETES MELLITUS *

By MARTIN H. REINBERG, M.D., and MORRIS LIPSON, M.D.,
Los Angeles, California

RECENT studies have indicated that the fatty liver represents an early stage in the pathogenesis of Laennec's cirrhosis.[1, 2, 3] There is evidence of an increased amount of fat in the livers of diabetic animals [4, 5] and of uncontrolled diabetic patients.[6, 7] Thus the incidence of Laennec's cirrhosis associated with diabetes mellitus is of some interest.

Enlargement of the liver is considered to be common in diabetic patients and almost invariable in those with diabetic acidosis.[1] It has been assumed that the hepatomegaly is due primarily to gross fatty infiltration.[7, 8] Unfortunately, liver size must be estimated by its clinical palpability, percussion, or roentgenographic appearance. It has been noted [10] that the incorrect diagnosis of Laennec's cirrhosis is made occasionally because of the presence of a palpable liver in patients with diabetes mellitus.

The normal weight of the liver is given as 1,200 to 1,600 gm.[11] As long ago as 1896 [12] it was pointed out that the liver might be palpable without being greater than average weight. Later it was again shown that there is only a rough correspondence between liver size and palpability.[10, 13, 14] In addition, clinical determination of liver nodularity is not verified by necropsy in a large percentage of cases.[14] Our own results indicate that, although there is a fair correlation between the level of the liver edge clinically and pathologically (figure 1), this level bears no constant relationship to liver weight (figures 2 and 3). The palpability of the liver is unreliable evidence of hepatomegaly.

The literature concerning the incidence of Laennec's cirrhosis in diabetes mellitus is conflicting. Schleusner [9] found 45 cases (12.7 per cent) of Laennec's cirrhosis in 355 autopsies performed on patients who had been known to have diabetes. In 20 of the 45 cases the onset of the diabetes preceded that of the cirrhosis. Connor [19] reported two cases of cirrhosis associated with diabetes which came to autopsy. He used these cases to emphasize that cirrhosis of the liver occurs with more than usual frequency in diabetic patients.

Approaching the problem differently, Yeld [15] found two patients with diabetes mellitus out of 131 autopsied cases of Laennec's cirrhosis. Blumenau,[16] in a similar study of 126 autopsied patients with cirrhosis, found four cases with diabetes mellitus. Robert [17] found an incidence of 7.6 per

* Received for publication October 25, 1948.
From the Departments of Pathology and Medicine, Los Angeles County Hospital, Los Angeles, California.

cent diabetes mellitus in 118 necropsied cirrhotics. In his series, the incidence of diabetes in noncirrhotics was 2.4 per cent. In Rabl's series of 275 autopsied cirrhotics,[18] there were three diabetics. Ratnoff and Patek,[10]

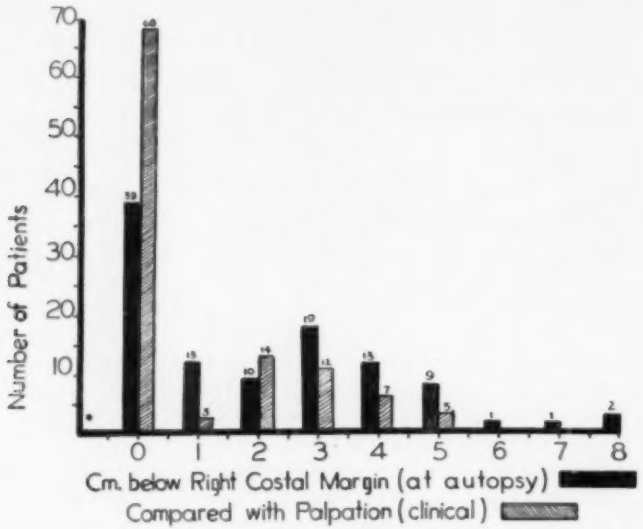


FIG. 1. Comparison of lower edge of liver pathologically with that found by clinical palpation in 107 unselected cases.

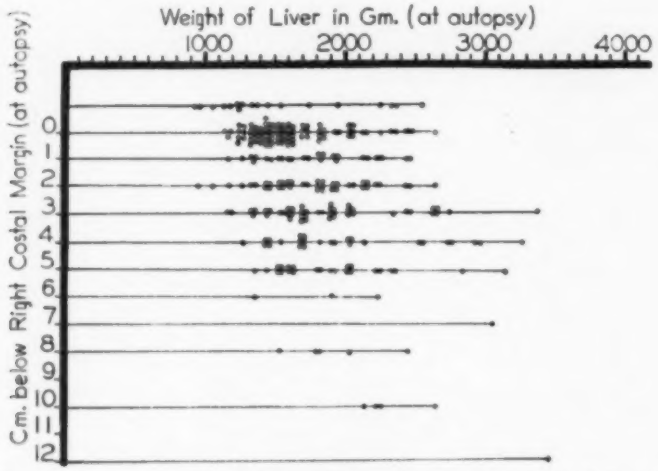


FIG. 2. Comparison of lower edge of liver at autopsy with weight of liver in 285 unselected cases.

in an extensive and excellent analysis of 386 cases of Laennec's cirrhosis, 178 of which were confirmed histologically, discovered that 5 per cent had diabetes mellitus, an incidence which they considered high.

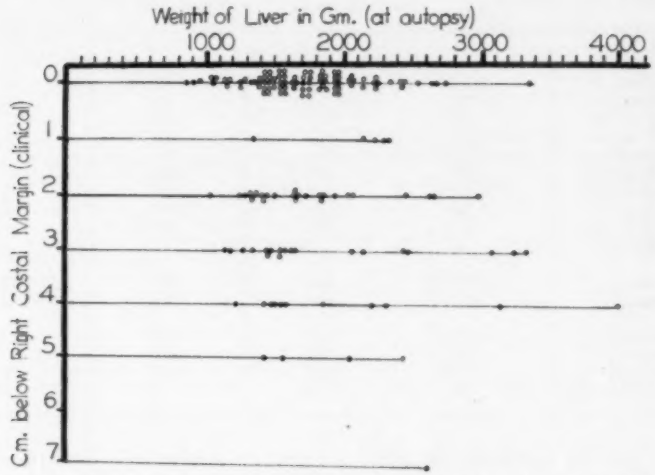


FIG. 3. Comparison of lower edge of liver as palpated clinically with weight of liver in 154 unselected cases.

At the Mayo Clinic, Wilder [7] found that only 17 (0.7 per cent) of 2,584 clinical cases of diabetes had hepatitis or cirrhosis, and concluded that there was an infrequent association of the two conditions. At the George F. Baker Clinic, Joslin [8] encountered 52 cases of cirrhosis of the liver out of 10,235 diabetic admissions, an incidence of 0.51 per cent.

METHOD

All autopsied cases at the Los Angeles County Hospital from 1939 to 1946, inclusive, were reviewed. There were 15,450 necropsies during this period. Five hundred seventy-six, or 3.7 per cent of these, were patients with diabetes. The diabetic autopsy protocols were studied to determine the incidence of fatty livers and of Laennec's cirrhosis. In all questionable cases the microscopic sections were reëxamined. Cases of hemochromatosis were excluded. Fatty livers were so called on the basis of gross description and microscopic appearance with hematoxylin and eosin stains. In only an insignificant number of cases were there fat stains. Consequently, the incidence of fatty livers in this series is subject to question. In those cases in which cirrhosis was diagnosed, concomitant fatty change in the liver was excluded from the fatty liver group. Five hundred seventy-six consecutive non-diabetic autopsies (1946) were utilized as a control group

TABLE I

Statistics on Total Autopsies from 1939 to 1946, Inclusive

Total	Entire Series 15,450	Nondiabetic Cirrhotics 744 (5.0%)	Diabetics 576 (3.7%)	Nondiabetic Controls 576
Age Groups				
0 to 9	2,349	1	0	99
10 to 19	352	1	10	17
20 to 29	616	18	13	17
30 to 39	1,096	103	21	36
40 to 49	1.679	193	59	77
50 to 59	2.532	175	144	73
60 to 69	3 077	145	175	107
70 to 79	2,708	82	131	114
80 to 89	975	24	22	34
90 to 99	66	2	1	2
Males	9,603	533	267	345
Females	5,874	244	309	281
Caucasian	12,276	621	482	420
Negro	1,185	34	42	63
Mexican	1,830	83	46	85
Miscellaneous	189	6	6	8

(table 1). In addition, the total number of nondiabetic cirrhotics from 1939 to 1946, inclusive, was determined.

RESULTS

Fatty Livers: In the diabetic group of 576 cases, 112, or 19.4 per cent, had fatty livers. In the control group of nondiabetics there were 87 (15.1 per cent) fatty livers (table 2). One hundred two (17.7 per cent) of the diabetic patients were in coma or acidosis prior to death. Fifty-two (51.0 per cent) of these had fatty livers. Of the remaining 474 (82.3 per cent) without coma or acidosis, only 60 (12.7 per cent) had fatty livers.

Cirrhosis: Thirty-three (5.7 per cent) of the total group of diabetics were proved cases of Laennec's cirrhosis. In comparison, 37, or 6.4 per cent, of the nondiabetic control group and 744, or 5.0 per cent, of the entire nondiabetic series had cirrhosis. However, these figures include a large

TABLE II

Comparative Incidence of Fatty Livers in Diabetics and Nondiabetic Controls

	Diabetics			Nondiabetics Total
	With Coma or Acidosis	Without Coma or Acidosis	Total	
Patients	102	474	576	576
Fatty Livers	52 (51.0%)	60 (12.7%)	112 (19.4%)	87 (15.1%)

number of stillbirths and infant deaths in the nondiabetic groups, whereas there were no autopsied diabetic cases in the 0 to 9 age group. Furthermore, there was only one case of cirrhosis in the 0 to 9 age group out of 14,874 nondiabetic necropsies. Thus a more valid comparison might be drawn if the 0 to 9 age group were eliminated. Excluding this, there were still 576 diabetics, with a 5.7 per cent incidence of Laennec's cirrhosis; there were 477 nondiabetic controls, with a 7.9 per cent incidence, and 12,525

TABLE III

Incidence of Cirrhosis in Diabetics and Nondiabetics

Total	Diabetics 576	Nondiabetic Controls 576	Nondiabetic Entire Series 14,874
Total with Cirrhosis	33 (5.7%)	37 (6.4%)	744 (5.0%)
Males	20	19	533
Females	13	18	244
Caucasian	23	30	621
Negro	1	2	34
Mexican	8	5	83
Miscellaneous	1	0	6
Age Groups			
0 to 9	0	0	1
10 to 19	0	0	1
20 to 29	0	0	18
30 to 39	1	4	103
40 to 49	3	17	193
50 to 59	8	7	175
60 to 69	12	4	145
70 to 79	8	3	82
80 to 89	1	2	24
90 to 99	0	0	2

TABLE IV

Corrected Incidence of Cirrhosis (Excluding Age Groups 0 to 9)

	Diabetics	Nondiabetic Controls	Nondiabetic Entire Series
Total (excluding ages 0 to 9)	576	477	12,525
Number of cirrhotics (excluding ages 0 to 9)	33	37	743
Corrected per cent of cirrhotics	5.7	7.9	5.9

nondiabetics in the entire series with a 5.9 per cent incidence of cirrhosis (table 4).

There was a total of 777 cases of cirrhosis in the entire series of 15,450 autopsies. Of these, 4.4 per cent also had diabetes mellitus.

Chronic Alcoholism: The incidence of chronic alcoholism in both groups of patients with cirrhosis was thought to be of some interest. Chronic alcoholism was considered to be present when there were repeated hos-

pital entries for acute alcoholism and/or when there was excessive daily alcohol intake. This intake most often amounted to an admitted pint to quart of whisky and/or an even larger volume of wine daily. It was found that eight, or 24.2 per cent, of the 33 diabetics with cirrhosis were chronic alcoholics (table 5). Four, or 12.1 per cent, denied chronic alcoholism. In

TABLE V

Incidence of Chronic Alcoholism in Cirrhotics

	Diabetics	Nondiabetic Controls
Total cirrhotics	33	37
Chronic alcoholics	8 (24.2%)	29 (78.4%)
Alcoholism denied	4 (12.1%)	4 (10.8%)
Not stated	21 (63.7%)	4 (10.8%)

21 cases (63.7 per cent), the presence or absence of chronic alcoholism was not stated. In contrast, 29, or 78.4 per cent, of the 37 nondiabetics with cirrhosis were chronic alcoholics. Four (10.8 per cent) denied chronic alcoholism. In only four (10.8 per cent) was there no statement as to alcoholic intake. This incidence of chronic alcoholism in Laennec's cirrhosis agrees with the figures given by Hall and Morgan in a previous study at this hospital.[5]

In order that the present series might better be compared to clinical studies such as those of Wilder [7] and Joslin,[8] an attempt was made to determine the frequency of correct diagnosis of Laennec's cirrhosis before death. It was found that the diagnosis was made in only seven (1.2 per cent) of the 576 diabetics (table 6). This is comparable to the incidences reported by them. In the control group of 576 nondiabetics, the diagnosis was made clinically in 24 cases (4.2 per cent).

TABLE VI

Clinical Diagnosis of Cirrhosis Compared with Autopsy Incidence

	Diabetics	Nondiabetic Controls
Total cases	576	576
Cirrhosis clinically diagnosed	7	24
Per cent of total cases clinically diagnosed as cirrhosis	1.2	4.2
Cirrhosis proved at autopsy	33	37
Number of times greater incidence cirrhosis at autopsy than clinically	4.7	1.5

DISCUSSION

Our results agree with previous studies [4, 5, 6, 7] which have shown an increased amount of fat in the livers of uncontrolled diabetics. The known incidence of chronic alcoholism is significantly higher in the nondiabetics with cirrhosis than in the diabetics with cirrhosis. However, there is a significantly higher percentage of diabetics with cirrhosis, in comparison to the control group of nondiabetics with cirrhosis, who had no data on

their histories concerning alcoholic intake. This may be due to a general assumption that diabetics for the most part refrain from excess alcoholic intake. If we, too, assume that the incidence of chronic alcoholism in diabetic patients is markedly lower than that in the general population (an assumption which may be unwarranted), then we must conclude that alcoholism plays at most a minor rôle in the pathogenesis of cirrhosis in diabetics. It is not within the scope of this paper to discuss further the possible relationships between the metabolic upset, fatty liver, and cirrhosis in diabetes.

The incidence of cirrhosis in diabetics as found by clinical studies is much lower than found at necropsy. In our own series, the incidence at autopsy is 4.7 times that found clinically. In the control group the autopsy incidence is only 1.5 times that found clinically (table 6). It is apparent from our results that there is no significant difference in the verified incidence of cirrhosis in diabetics and in nondiabetics. However, the diagnosis is not made sufficiently often in diabetics clinically.

Summary and Conclusions

1. A total of 15,450 autopsy protocols at the Los Angeles County Hospital, from 1939 to 1946, inclusive, were reviewed. Of these, 576, or 3.7 per cent, were diabetic.

2. Evidence was presented to show that clinical evaluation of liver size is unreliable. This was done with special reference to the clinical diagnosis of fatty liver or cirrhosis.

3. The increased incidence of fatty livers in uncontrolled diabetics was confirmed. This may be a factor in the pathogenesis of Laennec's cirrhosis in diabetes mellitus.

4. The rôle of alcoholism in the pathogenesis of cirrhosis in diabetics as compared with nondiabetics was briefly discussed.

5. Thirty-three, or 5.7 per cent, of the 576 diabetics had Laennec's cirrhosis. Thirty-seven, or 6.4 per cent, of the nondiabetic controls also showed cirrhosis. Correcting for a large number of stillbirths and infant and child deaths brought the incidence to 5.7 per cent and 7.9 per cent, respectively. In the entire series from 1939 to 1946, excluding diabetics, there were 744 cases of cirrhosis, an incidence of 5.0 per cent. Correcting as above brought this to 5.9 per cent.

6. There were 4.7 times as many diabetics with cirrhosis and 1.5 times as many nondiabetics with cirrhosis found at autopsy as were found clinically.

7. There is no significant difference between the incidence of Laennec's cirrhosis associated with diabetes mellitus and the incidence of cirrhosis in nondiabetics.

BIBLIOGRAPHY

1. Peters, J. P., and Van Slyke, D. D.: Quantitative clinical chemistry, Vol. I, 1946, The Williams and Wilkins Company, Baltimore.

2. Chaikoff, I. L., Connor, C. L., and Biskind, G. R.: Fatty infiltration and cirrhosis of the liver in depancreatized dogs maintained with insulin, Am. J. Path. **14**: 101–110, 1933.
3. Hall, E. M., and Morgan, W. A.: Progressive alcoholic cirrhosis, Arch. Path. **27**: 672–690, 1939.
4. Minkowski, O.: Diabetes mellitus nach Pankreasextirpation, Arch. f. exper. Path. u. Pharmakol. **26**: 371–387, 1889.
5. Allen, F. N., Bowie, D. J., Macleod, J. J. R., and Robinson, W. L.: Behaviour of depancreatized dogs kept alive with insulin, Brit. J. Exper. Path. **5**: 75–83, 1924.
6. Marble, A., White, P., Bogan, I. K., and Smith, R. M.: Enlargement of the liver in diabetic children. I. Its incidence, etiology and nature, Arch. Int. Med. **62**: 740–750, 1938.
7. Wilder, R.: Clinical diabetes mellitus and hyperinsulinism, 1940, W. B. Saunders Company, Philadelphia.
8. Joslin, E. P., et al.: Treatment of diabetes mellitus, 1946, Lea and Febiger, Philadelphia.
9. Schleusner: Ueber die Zusammenhange zwischen Diabetes mellitus und Erkrankungen der Leber und der Gallenwege, 1938, Herman Bauer, Marburg-Lahn.
10. Ratnoff, O. D., and Patek, A. J., Jr.: The natural history of Laennec's cirrhosis of the liver. An analysis of 386 cases, Medicine **21**: 207–268, 1942.
11. Lewis, H. L.: Gray's Anatomy, 1936, Lea and Febiger, Philadelphia, 1176.
12. Foxwell, A.: Alcoholic cirrhosis of the liver, Brit. M. J. **1**: 393–395, 1896.
13. Eppinger, H.: Leberzirrhose vom Standpunkte des Internisten, Arch. f. Verdauungskr. **36–37**: 143–144, 1925–1926.
14. Lichtman, S. S.: Diseases of the liver, 1942, Lea and Febiger, Philadelphia, 213–215.
15. Yeld, R. A.: Alcoholic cirrhosis, St. Barth. Hosp. Rep. **34**: 215–229, 1898.
16. Blumenau, E.: Ueber Todesursache bei Lebercirrhose, Arch. f. Verdauungskr., Berl. **27**: 1–17, 1920.
17. Robert, P.: Ueber Lebercirrhose, Comptes rendus de la premiere conference internationale de pathologie geographique, Geneva, 1931, Annex, 313–367.
18. Rabl, R.: Geographisch-pathologische Untersuchungen über Ikterus, acute gelbe Leberatrophie, Leberzirrhosen und Cholelithiasis. Ein Beitrag zu ihren Ursachen und Krankheitsbeziehungen, Arch. f. Schiffs-u. Tropen-Hyg. (Beihft. 1) **38**: 3–80, 1934.
19. Connor, C. L.: Fatty infiltration of the liver and the development of cirrhosis in diabetes and chronic alcoholism, Am. J. Path. **14**: 347–364, 1938.

THE LIVER BIOPSY: AN ANALYSIS OF PATHOLOGICAL FINDINGS IN 75 CASES *

By JULIAN HOFFMAN, M.D., and JULIUS ROSENTHAL, M.D.,
New York, N. Y.

ABNORMALITIES of the liver are frequently encountered both clinically and pathologically. Their clinical evaluation is complex because there is no single test adequate for the detection of all the functional abnormalities of the liver. For such study a battery of tests [1] is needed, and even then a complete answer is not always obtainable, since any one function of the liver may be altered while the others may remain comparatively normal. The growing volume of literature concerning functional and diagnostic studies of the liver attests to the importance of the subject.

In recent years, liver biopsy has been employed by an increasing number of investigators as an aid in the diagnosis of liver pathology. Davis,[2] Hoffbauer,[3] Buck,[4] Kumpe,[5] Franklin,[6] and their coworkers all report this procedure to be of value. Having dealt with this problem, we undertook a review of the liver biopsies done at Goldwater Memorial Hospital in order to ascertain the correlation between the clinical pictures and the histologic findings.

Since 1939, liver biopsies have been performed on 75 patients. Of these liver biopsies, 30 were surgical, two were peritoneoscopic, and 43 were needle. Surgical biopsies were performed during the course of various abdominal operations or as independent surgical procedures. Peritoneoscopic biopsies were done as described by Benedict.[7] Most of the needle biopsies performed in this hospital were done by the transthoracic approach described by Iverson and Roholm,[8] using the Silverman needle. According to Kumpe et al., this is the most satisfactory method. It appears that the needle biopsy is generally safer when there is liver enlargement. There is no contraindication to liver biopsy in the absence of a bleeding tendency. Even cardiac decompensation is not a deterrent, provided there is no laboratory evidence of a bleeding diathesis.

Of the three types of biopsy, the needle biopsy offers the simplest method of obtaining material. On the other hand, the amount of tissue removed is smaller than that obtained by surgical means (a few cubic millimeters compared with a cubic centimeter); moreover, the operator doing a needle biopsy cannot visualize the liver area most likely to show pathology. Despite these shortcomings, however, needle biopsy is of great value since it frequently provides a definite diagnosis. Our experience with peritoneoscopic

* Received for publication December 5, 1948.
From the Department of Pathology and the Second Medical Division of Goldwater Memorial Hospital.

biopsy is too limited to warrant conclusions. Reports by McHardy [9] and Benedict,[10] however, indicate its usefulness as a diagnostic aid. In a series of 50 cases, McHardy found peritoneoscopy, done together with needle biopsy, to be accurate in 96 per cent of the cases, whereas the clinical diagnosis was proved correct in only 56 per cent.

Hazards of Liver Biopsy

While the liver biopsy is usually a safe procedure, it must nevertheless be approached with caution. This applies to surgical as well as to needle biopsies, although to a much less degree in the former. In one of our cases, the surgeon performing a liver biopsy during a laparotomy observed considerable bleeding and had to suture the liver to arrest it. In one case in which needle biopsy had been done, blood was found in the ascitic fluid at the postmortem examination. However, the cause of death in this case was carcinoma of the liver. In a third case, the cause of death was ascribed directly to a needle biopsy done for the differential diagnosis of jaundice. The patient died three days later. At autopsy a bile peritonitis was found, apparently caused by the needle's entering an obstructed and dilated intrahepatic biliary duct producing oozing and bile peritonitis.

Material and Methods

The histologic findings of these liver biopsies were analyzed and compared with data obtained from other sources, including postmortem examination, laboratory findings, operative reports, and subsequent clinical course. It must be stated that the clinical diagnosis was known to the pathologist at the time the biopsies were originally reported.

Table I

Analysis of 75 Liver Biopsies

	Total Biopsies	Surg. Confirmation	P.M. Confirmation	Clinical Confirmation	Total Correlation	Inadequate Biopsy	Unconfirmed	Discrepancies
Needle	43	2	5	28	34	5	2	2
Surgical	30	20	6	20	24	0	5	1
Peritoneoscopy	2	0	1	1	1	0	1	0
	75	22	12	49	59	5	8	3

In the tables presented below, the term "surgical confirmation" is used when the surgeon's gross findings coincided with the histologic diagnosis. "Postmortem corroboration" refers to histologic diagnosis following autopsy. A case was considered confirmed by subsequent clinical findings if further laboratory findings and clinical diagnosis agreed with the histologic diagnosis after clinical observation for some time. "Total correlation" refers to the

total number confirmed by surgical, clinical or postmortem findings. In some cases, confirmation was obtained from all three sources, and therefore total correlation is not a sum of the three confirmations. In some cases the amount of tissue was too small to allow histologic interpretation, and these cases were so listed. Some cases were considered neither confirmed nor denied because of the lack of additional information following biopsy. In a certain number, there was a disagreement between the biopsy diagnosis and subsequent clinical course or autopsy diagnosis; these were listed as discrepancies.

The total number of autopsies in the biopsied cases in this series was 18. There were three autopsies on patients whose biopsies were inadequate because insufficient tissue was obtained for histologic study. Of the 15 autopsies performed on patients whose biopsies had been adequate for histologic study, there was agreement between biopsy and autopsy diagnoses in 12. In three cases there was a difference in diagnosis, and these are later described under "Discrepancies." The diagnoses in the 15 cases autopsied are listed below in table 2.

TABLE II

Postmortem Findings and Liver Biopsy Diagnosis

Case Nos.	Liver Biopsy Diagnoses	Postmortem Findings
45	Chronic passive congestion	Same
8	Metastatic carcinoma of liver	Same
9	Metastatic carcinoma of liver	Same
17	Laennec's cirrhosis	Same
18	Laennec's cirrhosis	Same
20	Laennec's cirrhosis	Same
22	Laennec's cirrhosis	Same
31	Capsulitis	Metastatic carcinoma of liver*
33	Pericholangitis	Same
40	Fibrosis	Cirrhosis*
47	Laennec's cirrhosis and primary hepatoma	Same
50	Disseminated lupus erythematosus	Same
51	Pericholangitis	Same
57	Perihepatitis	Metastatic carcinoma of liver*
62	Laennec's cirrhosis	Same

* These cases are discussed under discrepancies.

The biopsies were further analyzed according to the actual histologic diagnoses made. This summary appears in table 3.

The following results were obtained in the 75 liver biopsies:

Of 30 surgical biopsies, 24 (80 per cent) were confirmed either by clinical findings or postmortem examination. Of 43 needle biopsies, 34 (79 per cent) were confirmed by similar criteria. Of two peritoneoscopic biopsies, one was confirmed by autopsy findings. Six surgical biopsies were unconfirmed and one disagreed with clinicopathologic findings. Five needle biopsies were inadequate, one was unconfirmed, and two disagreed with clinical findings (table 1).

From an analysis of the above figures, one can conclude that biopsy has a distinct value in the diagnosis of liver pathology. This value can be further summarized under three headings:

1. *Cirrhosis.* There were 32 cases in which the histologic diagnosis of cirrhosis was made. The tissue was obtained by needle biopsy in 21 cases, by surgical biopsy in 10 cases, and by peritoneoscopy in one case. Confirmation by clinical or autopsy findings was obtained in 31 cases. In 12 of these, the diagnosis was determined prior to the establishment of a clinical diagnosis, although in a number of these cases this diagnosis had been suspected. In one case, the histologic diagnosis was not confirmed. This biopsy was

TABLE III

	Path Diag.	Clinical Diag.	Surg. Confirm.	P.M. Confirm.	Clinical Correl.	Discrep. Unconfirm. Inadequate	Type Biopsy		
							N	S	P
Cirrhosis—portal	32	26	6	5	31	1	21	10	1
Cirrhosis—biliary	2	2	2	0	2	0	0	2	0
Fatty liver	3	1	1	0	3	0	2	1	0
Carcinoma									
a. Primary	1	1	0	1	1	0	1	0	0
b. Metastatic	6	2	5	2	6	0	1	5	0
Pericholangitis	4	4	3	2	4	0	1	3	0
*Hepatitis	11	3	3	0	3	8	5	6	0
Amyloidosis	1	1	0	0	1	0	1	0	0
Boeck's sarcoid	1	1	1	0	1	0	0	1	0
Chr. passive congest.	1	1	0	1	1	0	0	1	0
† Lupus erythematosus	1	1	0	1	1	0	1	0	0
Normal liver	7	5	1	0	5	2	5	1	1
Inadequate biopsies	5	0	0	0	0	5	5	0	0
	75	48	22	12	59	16	43	30	2

* Under this heading there were two cases diagnosed histologically as periportal focal hepatitis and one case of periportal fibrosis. The subsequent clinical course (and in one case the autopsy findings) was that of cirrhosis. Two other cases diagnosed histologically as hepatitis were later found to be cases of carcinoma. These will be discussed under the title "Discrepancies."

† The diagnosis was made as compatible with the clinical diagnosis of disseminated lupus erythematosus.

obtained at operation for carcinoma of the colon. The liver was described as grossly normal, but histologic section showed early cirrhotic changes. The patient died but autopsy was not performed. The final status of the liver was therefore not determined. In three cases clinically diagnosed as cirrhosis, biopsy failed to provide definite confirmation, the pathologic findings having been (1) perifocal hepatitis with fibrosis suggestive but not diagnostic of cirrhosis; (2) fibrosis and lymphocytic infiltration inadequate for diagnosis of cirrhosis; (3) focal periportal hepatitis and congestion. These discrepancies will be discussed below.

2. *Carcinoma of the Liver.* There were seven cases in which a biopsy diagnosis of carcinoma of the liver was made. Needle biopsy was used

to obtain the tissue in one case of primary carcinoma (hepatoma) and in one metastatic lesion, while surgical biopsy was the source of material in five cases of metastatic carcinoma of the liver. Post mortem confirmed the diagnosis in three and operation was confirmatory in the other four. In another case (Case 57), surgical exploration was done on suspicion of abdominal malignancy. A lymph node removed at operation was reported as showing metastatic carcinoma. The liver showed no evidence of malignancy at operation, and biopsy revealed only focal hepatitis. The patient died six months later. Autopsy showed bronchogenic carcinoma with extensive liver metastases. It is very probable that biopsy taken six months previously was from a portion of uninvolved liver.

Although this series is small, it is clear that a positive diagnosis of carcinoma of the liver can be made by biopsy. The value to the clinician is obvious, particularly in those cases in which a needle biopsy will furnish a definite diagnosis. Even in the face of expanding criteria for cancer surgery, the finding of a metastatic lesion in the liver will be important as a guide in the contemplation of extensive surgery. On the other hand it must be noted, of course, that a negative biopsy is inconclusive in that it may be taken from the uninvolved portion of the liver, as in Case 57. This is most likely to occur with needle biopsy, but it has even occurred with biopsy taken under direct visualization, as in one case (Case 4) in this series, in which metastatic nodules were seen on peritoneoscopy but only normal liver was found on microscopic study.

3. *Other Conditions.* The liver biopsy was found to be of value in a number of other conditions. The diagnosis of Boeck's sarcoid was made in one, amyloidosis in another, and biliary cirrhosis in two others. But it is not alone in the establishment of a diagnosis that the liver biopsy is of value. It is equally useful in the exclusion of suspected diseases. Thus, in four cases of liver enlargement associated with cardiac decompensation, where the hepatomegaly was suspected of being caused by intrinsic liver disease rather than by congestion, biopsy eliminated the former possibility.

In addition to its function as a diagnostic aid, liver biopsy may also prove to be increasingly important in the evaluation of therapy of "alcoholic" and "toxic" cirrhosis, as well as in following the general course of liver disease. Chaikoff and Connor [12] have described very interesting results in the study of experimentally produced cirrhosis in animals. Although the use of serial biopsy in humans is limited, clinical studies have been reported. Beams [13] has described changes in the histologic picture in 14 patients treated for cirrhosis, nine treated with high protein, high vitamin diet, and five with this diet plus methionine. The author shows alteration in the microscopic picture, with significant decrease in pathology in four of the latter group of cases. Buck [4] has recently reported similar findings in five of seven alcoholics with incipient cirrhosis. In one case (Case 69) in our series to be described below, three biopsies were taken at intervals. The variations in the histologic

appearance are interesting because they reflect the course of the disease. It is in such instances that liver biopsy offers possibilities in the investigation of fundamental processes in liver disease. At present, the evidence for the development of cirrhosis following hepatitis is almost entirely confined to chemical and clinical observations.[14] It is likely that follow-up liver biopsy studies may provide pertinent evidence concerning the relationship between hepatitis and cirrhosis.

Discrepancies

Of 75 biopsies examined, 59 (79 per cent) were corroborated by either surgery, clinical course, or postmortem examination. In 16 cases, biopsy diagnosis could not be correlated with clinical and autopsy data. In five of these 16 cases, the biopsies were inadequate. In the other 11, different diagnoses were made. This disagreement was not necessarily due to an error in the histologic diagnosis; in eight of these cases, the tissue diagnosis was not definitely confirmed or denied by the subsequent course. Four of the eight patients died without autopsy examination. In two of the eight cases, the interval between biopsy and death was too long to permit a comparison between the two tissues. The other two patients are still alive and, in their cases, there is still a question of clinical diagnosis. In three of the 11 cases, there was a discrepancy between the biopsy report and the sub-

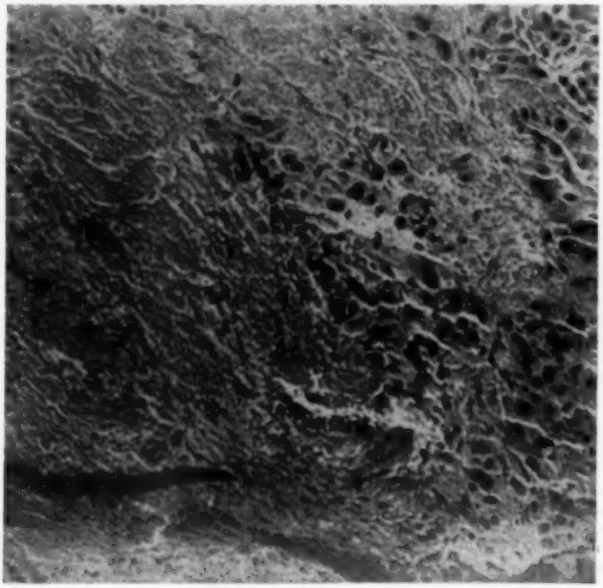


Fig. 1. Needle biopsy. Diagnosis: Cirrhosis, hepatoma. H & E stain. 500×.

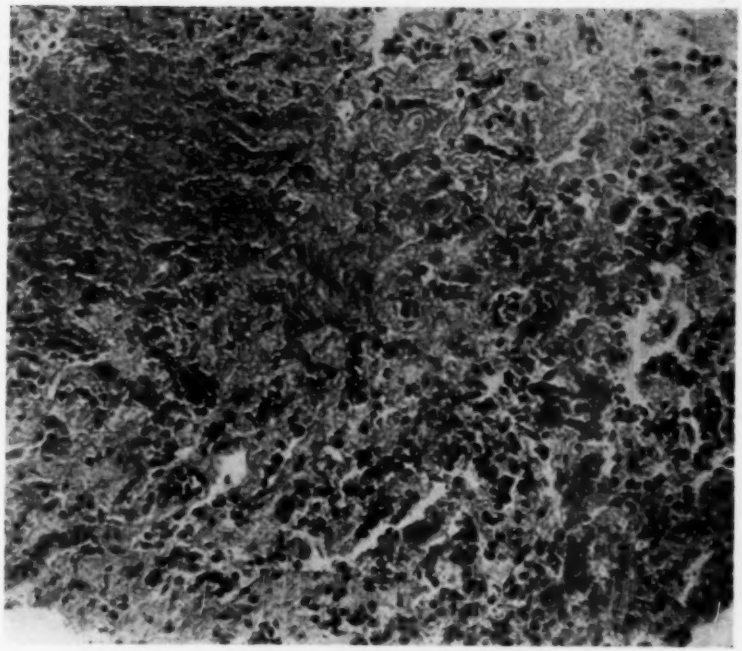


FIG. 2. Needle biopsy. Diagnosis: Metastatic carcinoma. H & E stain. 500×.

sequent findings. However, the disagreement was not one of fundamental pathology but rather of the degree of lesion, the pathologic diagnoses having been, respectively, periportal hepatitis, periportal fibrosis, and hepatitis with fibrosis, while the subsequent findings indicated that the patient actually had portal cirrhosis. These three cases are described below (Cases 40, 63 and 70).

CASE REPORTS

Case 40. This patient was admitted with hepatosplenomegaly and a temperature of 103° F. Laboratory studies showed an anemia and impaired liver function. Liver biopsy showed fibrosis and lymphocytic infiltration, "inadequate to diagnose cirrhosis." This is considered a discrepancy, since autopsy showed Laennec's cirrhosis.

Case 63. This 45 year old white man was transferred from Bellevue Hospital, where a diagnosis of cirrhosis had been made because of a 28 year history of excess alcoholism and a recent development of ascites. In this hospital a barium enema showed a polypoid cecal lesion, and the patient was therefore subjected to surgery. At operation the patient had ascites and a large nodular liver. There was no cecal lesion. Needle biopsy taken at operation showed periportal fibrosis and focal hepatitis, suggestive but not diagnostic of portal cirrhosis. The patient died but autopsy was not performed. The final clinical diagnosis was Laennec's cirrhosis. The discrepancy in this case is due to interpretation rather than to basic pathology.

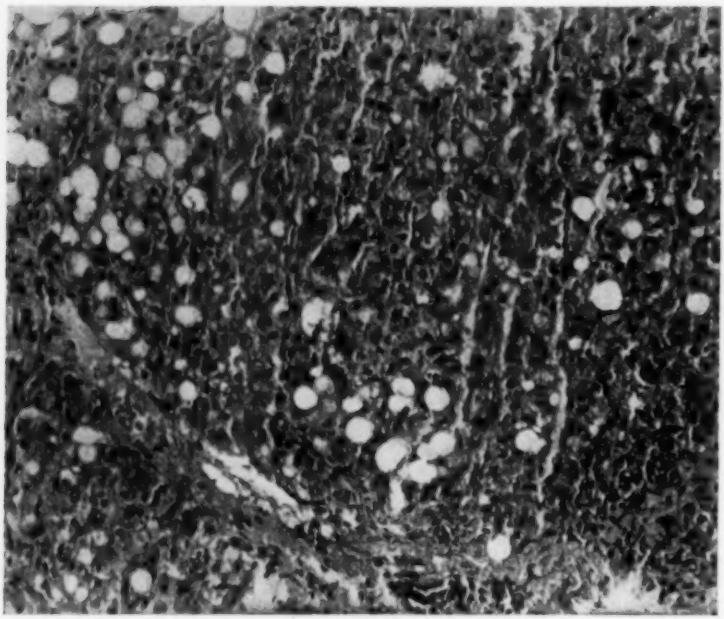


FIG. 3. Needle biopsy. Diagnosis: Portal cirrhosis and fatty liver before treatment, December, 1947. H & E stain. 500 ×.

Case 73. This patient was admitted for cardiac decompensation, jaundice, and a history of coronary artery disease. On physical examination he was found to have an enlarged liver, bilateral pleural effusions, and peripheral edema. While in the hospital he had several hemoptyses and fluctuating jaundice. His bromsulfalein tests showed abnormal retention, but his cephalin flocculation test was negative. Liver biopsy showed congestion and focal periportal hepatitis. The present clinical diagnosis is portal cirrhosis. This case is listed as a discrepancy because of the subsequent clinical diagnosis of portal cirrhosis. However, the clinical diagnosis has not been entirely confirmed.

Case 56. A 64 year old man was admitted to Goldwater Memorial Hospital with a diagnosis of central nervous system lues with Charcot's joint. While in the hospital he developed intense painless jaundice. On examination there was tenderness deep in the epigastrium and the spleen was palpable. Laboratory studies showed 4 plus bile in the urine and a trace of urobilinogen. Two days later it was noted that the jaundice was deeper, the stool was clay colored, bile was 2 plus in the urine, and there was no urobilinogen. White blood count was 6,000, icterus index 46, and cephalin flocculation plus 4. A history of transfusions four months previously was then noted. Liver biopsy showed "cirrhosis of the liver with biliary obstruction, apparently due to hepatitis." The patient was treated conservatively and made a complete clinical recovery. Five months later the patient gave no clinical evidence of jaundice or recurrent biliary obstruction.

The liver biopsy in this case established a differential diagnosis between intrahepatic and extrahepatic jaundice. The need for surgery was therefore obviated by this diagnostic procedure.

Case 47. A 68 year old white man was admitted to Goldwater Memorial Hospital with a diagnosis of cirrhosis. His past history revealed chronic alcoholism. For two years prior to admission his condition had been progressively downward. On physical examination the skin was icteric, the liver was palpable, and fluid was noted in the abdomen. Laboratory tests revealed a plus 3 cephalin flocculation. Total blood bilirubin was 2.4 mg. per cent. Biopsy revealed Laennec's cirrhosis with superimposed primary carcinoma of the liver. This was confirmed at autopsy (figure 1).

This case illustrates the possibility of establishing a diagnosis of malignancy of the liver even in the presence of cirrhosis by means of liver biopsy.

Case 8. A 70 year old white male was admitted to Goldwater Memorial Hospital with the diagnosis of generalized arteriosclerosis. In the hospital he developed jaundice with bile in the urine. The icterus index was 105, cephalin flocculation plus 4. There was marked leukocytosis, and a diagnosis of liver abscess was made. Aspiration yielded necrotic material containing malignant cells. Local surgical biopsy confirmed

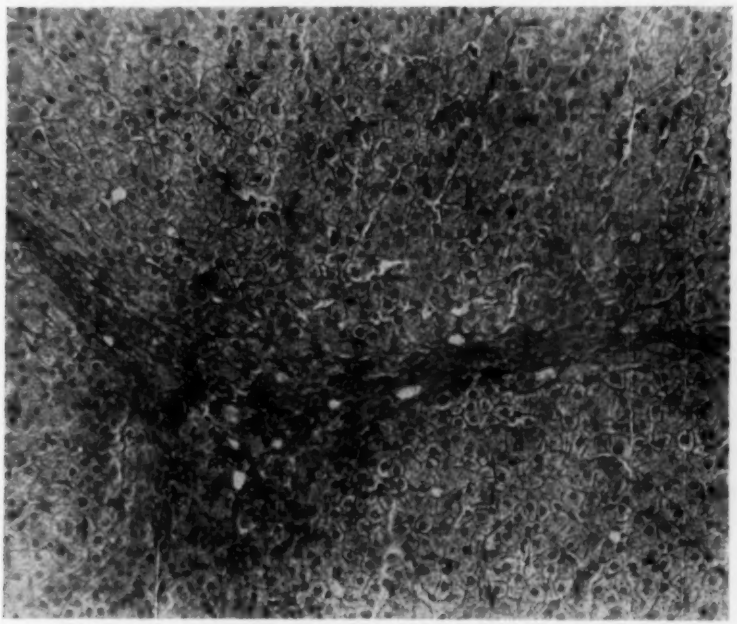


FIG. 4. Surgical biopsy. Diagnosis: Portal cirrhosis after treatment, March, 1948. Note decrease of fat. H & E stain. 500 ×.

the diagnosis. At autopsy, carcinoma of the gall bladder and liver was found (figure 2).

In this case, needle biopsy established the diagnosis of metastatic carcinoma, and major surgery was therefore avoided.

Case 69. This 46 year old white female was transferred from another hospital with a diagnosis of chronic hepatitis. She was admitted to that hospital with right lower quadrant pain and vomiting. The admission diagnosis was intestinal obstruction. This was excluded by roentgen-ray and subsequent clinical findings. During the course of investigation she was found to have an enlarged, tender liver and laboratory evidence of liver damage. Later biopsy showed essentially a moderate degree of portal cirrhosis and a large amount of fat deposition in the liver parenchyma (figure 3). On admission to Goldwater Memorial Hospital, a two year history of alcoholism and poor dietary intake was elicited. The liver and spleen were palpable. Laboratory tests showed bromsulfalein retention of 55 per cent in a half-hour and an icterus index of 6. Three months later, biopsy showed a marked regression in the amount of fat and a somewhat more cellular type of cirrhosis (figure 4). The portal space in this section showed relatively more cells and less connective tissue than in the previous biopsy. It was noted at this time that the patient showed

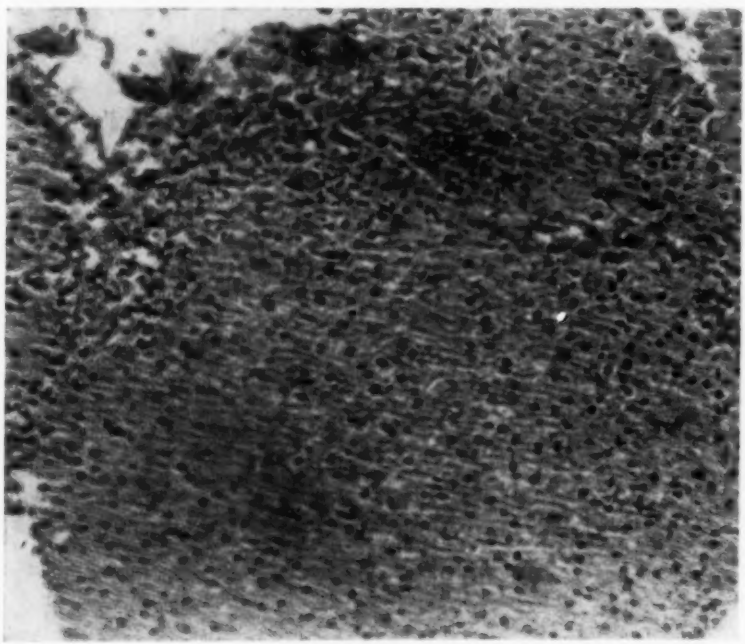


FIG. 5. Needle biopsy. Diagnosis: Portal cirrhosis three weeks later, April, 1948. Note almost no fat. H & E stain. 500×.

clinical improvement both in physical condition and in laboratory tests. Repeat biopsy one month later showed a minimum amount of fat and a moderate amount of cellularity and fibrous tissue (figure 5).

This case illustrates the changes in liver pathology that may be seen on serial sections. Such changes may reflect the course of the disease and the prognosis.

Summary and Conclusions

The liver biopsy has a definite place in the evaluation of the more severe type of liver pathology. Although a positive pathologic finding is more important than a negative one, a negative finding may at times be very valuable. The needle biopsy of the liver has gradually come to supplant the surgical biopsy because of its simplicity. It is a useful means of providing a diagnosis and is often as definite as a surgical biopsy. In some cases the surgical biopsy is to be preferred, either for technical reasons, as during the course of an exploratory abdominal operation, or when a larger amount of tissue is desired for diagnosis. The liver biopsy may also prove to be helpful eventually in evaluating the course of liver disease and the effect of therapy. The needle biopsy has a small but definite risk, and should only be done by those well trained in its performance.

BIBLIOGRAPHY

1. Bockus, H. L.: Gastroenterology, first edition, 1946, W. B. Saunders Co., Philadelphia, pp. 62–65.
   Mateer, J. G., and others: Chronic subclinical impairment of liver function, J. A. M. A. **133**: 909–916, 1947.
   Slay, H., and Siplet, H.: Minimal yet adequate program of liver function studies in the differential diagnosis of jaundice, Am. J. Med. **4**: 215–227 (Feb.) 1948.
2. Davis, W. D., Scott, R. W., and Lund, H. Z.: Needle biopsy of the liver, Am. J. M. Sc. **221**: 449–461, 1946.
3. Hoffbauer, F. W.: Needle biopsy, J. A. M. A. **134**: 666–670, 1947.
4. Buck, R. F.: Observations on alcoholic and fatty liver. The use of internal needle biopsy and liver function tests, J. Lab. and Clin. Med. **33**: 555–564, 1948.
5. Kumpe, W. D., Gall, E. A., Schiff, L., Molle, W., Safdi, S. A., and Sternberg, H. H.: Needle biopsy of the liver, Gastroenterology **9**: 672–681, 1947.
6. Franklin, M., Popper, H., Stergmann, F., and Kozoll, D. D.: Relation between structural and functional alterations of the liver, J. Lab. and Clin. Med. **33**: 435–448, 1948.
7. Benedict, E. B.: Peritoneoscopy, New England J. Med. **218**: 713–719, 1938.
8. Iverson, P., and Roholm, K.: Aspiration biopsy of the liver with remarks on its diagnostic significance, Acta med. Scandinav. **102**: 1–9, 1939.
9. McHardy, G., Browne, D. C. and Edwards, E.: Peritoneoscopic and biopsy evaluation of hepatic disease, Gastroenterology **9**: 682–685, 1947.
10. Benedict, E. B.: Peritoneoscopy in liver disease, New England J. Med. **230**: 125–130, 1944.
11. Babcock, W., and Bacon, H. E.: Complications in surgical treatment of cancer of the large bowel, J. A. M. A. **128**: 73–77, 1945.
12. Chaikoff, L. I., Connor, C. L., and Biskind, C. R.: Fatty infiltration and cirrhosis of the liver in depancreatized dogs maintained by insulin, Am. J. Path. **14**: 101, 1938.

13. Beams, A. J., and Endicott, E. T.: Histological changes in the livers of patients with cirrhosis treated with methionine, Gastroenterology **9**: 718–735, 1947.
14. Barker, M. H., Capps, R. B., and Allen, F. W.: Chronic hepatitis, J. A. M. A. **129**: 653–659, 1945.

Altschule, M. D., and Gilligan, D. R.: Chronic latent hepatitis following catarrhal jaundice, New England J. Med. **231**: 315–317, 1944.

Kornberg, L.: Latent liver disease in persons recovered from catarrhal jaundice and in otherwise normal medical students as revealed by bilirubin excretion test, J. Clin. Investigation **21**: 299–308, 1942.

Mallory, T. B.: Pathology of hepatitis, J. A. M. A. **134**: 655–661, 1947.

Editorial: Hepatitis, Ann. Int. Med. **24**: 511–516, 1946.

CLINICAL EXPERIENCES WITH A NEW MERCURIAL DIURETIC FOR SUBCUTANEOUS ADMINISTRATION *

By Joseph B. Vander Veer, M.D., F.A.C.P., P. T. Kuo, M.D., *Philadelphia, Pennsylvania,* and David S. Marshall, II, M.D., *Pottsville, Pennsylvania*

Organic mercurial compounds are the most powerful diuretics known. They have become an important agent in the treatment of edema, especially that of chronic congestive heart failure. DeGraff and his associates have shown that the addition of a theophylline group to the mercurial compounds enhances the diuretic effect of these substances and reduces their toxicity.[1] The three currently used preparations containing theophylline—Mercuzanthin, Salyrgan-theophylline, and Mercuhydrin—possess local irritating properties and require deep intramuscular or intravenous injections. With these routes of administration, a number of severe local reactions [2] and fatal cardiac toxicity [1, 3, 4, 5, 6] have been reported with the use of therapeutic doses of these preparations. Thiomerin, a new organo-mercury compound, is synthesized by replacing the theophylline radical in the Mercuzanthin molecule with a mercaptide. According to the few available experimental and clinical studies, the drug has been shown to be free from irritating properties when administered subcutaneously.[7, 9, 10, 19] It has been found to be from 160 to 200 times less toxic to the heart of experimental animals when it was administered intravenously.[8] The purpose of this report is to present our clinical experience with this diuretic in the treatment of patients with edema due to cardiac, renal, and hepatic diseases.

Material and Methods of Observation

This report includes a study of 106 in-patients and five ambulatory patients who required diuretic therapy because of edema, pulmonary congestion, and/or fluid in the serous cavities. All 106 patients were kept on bed-rest during the period of observation. One hundred and one of the total 106 in-patients in this series were receiving digitalis therapy, and 28 of these digitalized patients received aminophylline intravenously or per rectum at various times during their hospitalization. The five ambulatory patients were kept on maintenance doses of digitalis. All patients were on a limited sodium chloride intake. In the hospitalized patients this was less than 1 gm. per day. Ammonium chloride, 4 to 6 gm. per day, was given in inter-

* Received for publication September 6, 1949.
From the Department of Cardiology, Division of Medicine, Pennsylvania Hospital, Philadelphia, Pennsylvania.
The materials used in this study were supplied by Campbell Pharmaceutical Co., New York, New York.

rupted courses of three to four days each to 38 patients. Except in critically ill patients, where an early diuresis was considered essential, the mercurial diuretic was given only after three to four days' observation to note the effect of bed-rest and other types of therapy. One-half to 2 c.c. of Thiomerin solution at the concentration of 39 mg. of mercury per c.c. was then given to the patients subcutaneously in the deltoid area. Changes in the body weight, pulmonary congestion, and degree of dependent edema were carefully noted, preceding, during, and after the Thiomerin administration. Special attention was given to the detection of signs and symptoms of local irritation and to evidence of toxic effects on the heart, kidneys, and other organs of the body. In the course of this study, subcutaneous mercurial injections were temporarily interrupted in nine of the patients and equivalent amounts of Mercuzanthin were substituted by intramuscular injection. This was done to compare the relative effectiveness of these two preparations.

Clinical Diagnosis of This Series of Patients

The present series of patients includes 101 cases of heart disease of various etiologic types with congestive heart failure, four cases of Laennec's cirrhosis of liver with ascites and edema, three cases of malignant hyperten-

Table 1

The Clinical Diagnosis of this Series of 111 Patients

Clinical Diagnosis	Number of Cases
Arteriosclerotic heart disease	40
Rheumatic heart disease	20
Hypertensive heart disease	16
Arteriosclerotic and hypertensive heart disease	9
Syphilitic heart disease	8
Chronic cor pulmonale	5
Malignant hypertension	3
Laennec's cirrhosis of liver	4
Chronic glomerulonephritis	2
Congenital heart disease (Lutembacher's syndrome)	1
Adhesive pericarditis, chronic	1
Heart disease due to anemia	1
Generalized malnutrition with hypoproteinemia	1
Total	111

sion, two cases of chronic glomerulonephritis with nephrotic syndrome, and one case of nutritional edema. The detailed distribution of these 111 patients among the various clinical diagnoses is presented in table 1.

Dosage and Frequency of Administration

Doses of Thiomerin ranging from 0.5 c.c. to 2 c.c. were given daily or every second to fourth day to this group of patients, depending upon the condition of the patient and the response to therapy. Fifty-seven (or 51 per cent) of the patients received a 2 c.c. dose (1 c.c. in two sites) daily for periods varying from two to 37 days. Forty-one of these patients received

1 c.c. daily for three to 19 days. The majority received either 1 c.c. or 2 c.c. of Thiomerin daily for six to 10 days. The more detailed ranges of the dosage and frequency of administration of Thiomerin are presented in table 2.

The Onset of Diuresis

The diuretic response of 106 hospitalized patients was measured clinically by the loss of body weight following the administration of Thiomerin. Based on the above criterion, we found that satisfactory diuresis resulted in 78 of the 106 patients (or 73 per cent) within the first 24 hours of the subcutaneous injection of Thiomerin. Eighteen patients began to lose weight in the second 24 hour period, and in three others an appreciable weight loss was not evident until the third day after the injections had been begun. The response of the remaining seven patients was considered unsatisfactory.

Table II

Dosage and Frequency of Thiomerin Administration

Dosage Range	Frequency of Administration	Number of Cases
2 c.c.	Daily	57
2 c.c.	Every other day	6
2 c.c.	Every third day or every fourth day	4
1 c.c.	Daily	41
0.5 c.c.	Daily	3
Total		111

We have also observed that, although there was no great difference in the rate of onset of diuresis in the majority of patients who received 1 c.c. or 2 c.c. of Thiomerin daily, the clinical response was usually delayed when such small doses as 0.25 c.c. or 0.5 c.c. of the drug were used.

Diuretic Effect with Continued Administration of Thiomerin

When daily doses of Thiomerin were given, the majority of our patients showed a maximal loss of edema fluid during the second 24 hours after the therapy had been begun. The degree and duration of effective diuresis from the second day onward were found to be roughly proportional to the amount of edema then present in the individual patient. In about 70 per cent of our patients, a more or less stationary or "dry" weight was reached in from six to 10 days after the initiation of the diuresis. On the average, patients who received 2 c.c. of Thiomerin daily registered a loss of body weight of 2 to 6 pounds daily, with a range of 0 to 17 pounds. Less drastic diuresis was noted in patients who received 1 c.c. dose daily. The average weight loss in this latter group was 2 to 4 pounds, with a range of 0 to 9 pounds daily. The number of patients who were on a 0.5 c.c. daily dosage schedule and those who received 1 c.c. or 2 c.c. doses at one to three day intervals were too few to warrant a detailed analysis.

Residual Diuretic Effect after the Interruption of Therapy

Thiomerin administration was interrupted in 20 patients in this series and the daily weight of these patients was followed. The body weight of these patients was found either to remain stationary or to show a slight decline of 1 to 2 pounds for a short period following the interruption. The residual diuretic effect was demonstrable for a period of two days in 18 patients who were receiving 1 c.c. or 2 c.c. of Thiomerin a day. In one patient the diuretic effect was prolonged for three days and in another five days after the administration was stopped. Other patients, after responding satisfactorily to the treatment of edema, including adequate diuretic therapy, did not show a tendency to re-accumulate edema fluid after the termination of the therapy during the short period of observation before they were discharged from the hospital.

A Comparison of the Diuretic Effects of Thiomerin and Mercuzanthin

In order to compare the relative diuretic effect and characteristics of Thiomerin with Mercuzanthin, we substituted the subcutaneous mercurial with equivalent doses of Mercuzanthin intramuscularly in nine patients during diuretic therapy. Six patients received 2 c.c. of Mercuzanthin for three successive days, and the other three received 1 c.c. daily for three days. A study of the amount of diuresis as measured by weight loss in these nine patients showed that: (1) the diuretic effects of amounts of Thiomerin given subcutaneously were very similar to those of Mercuzanthin given intramuscularly in the same patient; (2) the rate of onset and the duration of action were also similar, and (3) Mercuzanthin administered intramuscularly appeared to cause more discomfort at the site of injection than subcutaneous Thiomerin. No objective findings of local irritation were observed in any of these patients so studied.

Case Report

The characteristic diuretic response to subcutaneous Thiomerin can be illustrated by the following case report:

A 61 year old Negro woman was admitted to the hospital on August 26, 1948, complaining of "swelling all over." She was known to have had hypertension for a number of years, and first began to experience shortness of breath and ankle edema in February, 1948. Despite digitalis, ammonium chloride and intravenous injections of Mercuzanthin at irregular intervals, her condition became progressively worse, and about 10 days prior to admission the edema had spread to involve the abdomen, chest and arms. Physical examination revealed the patient to be orthopneic and markedly edematous. The neck veins were greatly engorged. The chest wall and breasts were thick with edema fluid. The lungs were filled with numerous moist and wheezing râles. The heart was enlarged to the left with auricular fibrillation and had an irregular ventricular rate of approximately 90 per minute. A blowing grade III sys-

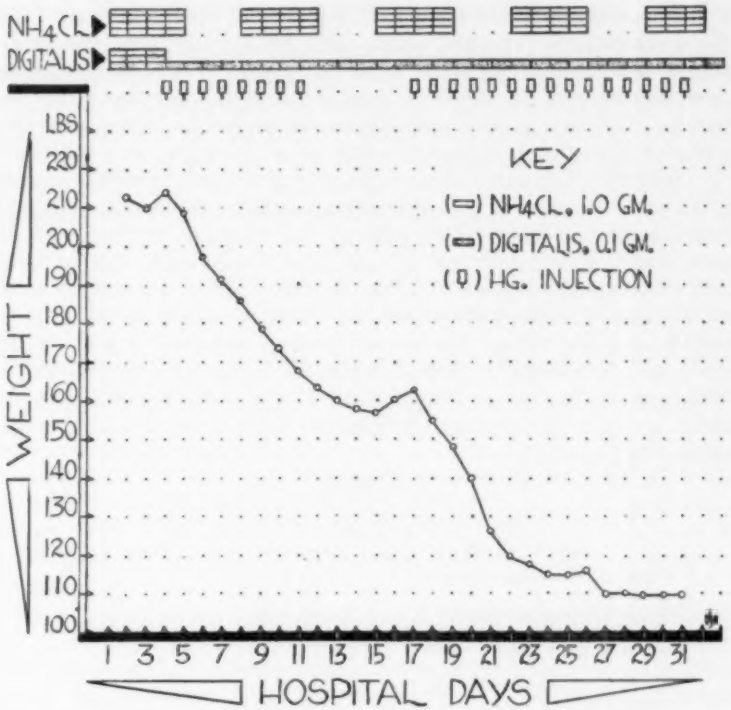


FIG. 1. Patient, M. J., a Negro woman, aged 61, was hospitalized because of hypertensive and arteriosclerotic heart disease with auricular fibrillation. Massive anasarca was present. She had previously been treated as an out-patient with the usual measures without relief. A marked diuresis with the loss of over 100 pounds of weight followed the use of Thiomerin in full dosage, subcutaneously. Each dose of the diuretic recorded on the chart represents 2 c.c. of solution.

tolic murmur was audible over the apex and the second sound was accentuated in the pulmonic area. The abdominal wall and the lower extremities showed extreme edema. She weighed 215 pounds on admission and did not show any appreciable weight loss after three days of bed-rest, additional digitalis therapy, ammonium chloride, aminophylline and salt restriction. Thiomerin in 2 c.c. doses daily was started on the fourth hospital day. The diuretic response was dramatic. The daily weight record of this patient is presented in figure 1. She lost a total of more than 100 pounds of edema fluid, and her weight became constant about the twenty-seventh hospital day.

TOXIC MANIFESTATIONS AND UNTOWARD REACTIONS

1. Local Reactions. Seven patients in this series of cases, who received a total of 891 subcutaneous injections of Thiomerin in 0.5 c.c. to 2 c.c. doses, complained of pain or burning at the sites of the injections. The discom-

fort was noted shortly after the injection and lasted for a few hours. Two of the seven patients developed tender indurations on the arm, and another a painful vesicle measuring about 1 cm. in diameter. All lesions improved without ulceration of the skin. In spite of the signs and symptoms of local irritation, all of these patients were able to tolerate further injections without any trouble when fresh solutions of a new lot of Thiomerin were substituted.

2. Systemic Reactions. Seven patients developed systemic reactions suggestive of dehydration and electrolyte imbalance while receiving 2 c.c. Thiomerin solution daily. Two patients had muscular cramps, weakness, nausea, vomiting, and diarrhea. In the other five patients, only symptoms of abdominal cramps and diarrhea were present. Blood urea nitrogen levels were elevated in four of these patients. The symptoms of salt depletion promptly disappeared and the blood chemistry returned to more normal levels when the mercurial administration was temporarily interrupted and sodium chloride was given. Small doses (1 c.c.) of Thiomerin were later resumed in these patients and satisfactory results were obtained without further complications.

TABLE III

Clinical Diagnosis of Cases Who Responded Poorly to Thiomerin

Clinical Diagnosis	Thiomerin Given	Number of Cases
Chronic glomerulonephritis with renal failure	2 c.c. daily for 5 days	1
Chronic pyelonephritis with with renal failure	1 c.c. daily for 3 days	1
Rheumatic heart disease, active	1 c.c. daily for 6 days	2
Malignant nephrosclerosis with renal failure	1 c.c. daily for 2 days	1
Rheumatic heart disease and anemia due to uterine hemorrhage	0.5 c.c. daily for 7 days	1
Acute coronary thrombosis	2 c.c. one dose	1
Total		7

Five doses of 2 c.c. and three doses of 1 c.c. of Thiomerin were given to two patients with hypertension, pulmonary congestion, peripheral edema, albuminuria and moderate degrees of nitrogen retention, in desperate attempts to initiate a diuresis. Both of these patients died shortly thereafter with increasing albuminuria and urinary elements and mounting nitrogen retention. A general macular eruption was observed in one of the patients about 24 hours before death. Postmortem examination was made on one of the patients and revealed an enlarged and hypertrophied heart and chronic pyelonephritis with few focal areas of tubular necrosis. In non-nephritic patients, serial urinalyses and blood urea nitrogen determinations revealed no evidence to suggest renal damage due to drug toxicity. Reactions due to hypersensitivity or toxicity to the heart were not observed in this series of cases studied.

Poor Response to Thiomerin Administration

In addition to the two cases of advanced renal disease with nitrogen retention mentioned, there were four other patients who did not show the expected diuretic response to subcutaneous Thiomerin. The clinical diagnosis of these cases and the amount of Thiomerin given are listed in table 3.

We found that patients with very low renal function usually respond poorly to Thiomerin. It is generally agreed that patients with renal disease with failure should not receive mercurial diuretics.

Discussion

In this study, a total of 891 subcutaneous injections of Thiomerin were given to 111 patients. Only seven instances of relatively mild local reactions were encountered. Most of these reactions were found to follow the injections of slightly cloudy solutions of the drug. The earlier lots of Thiomerin were relatively unstable in aqueous solution, and some cloudiness would often appear in four to six days. In all seven patients there were no further reactions when freshly prepared solutions of the drug were used. Our experiences, therefore, confirm the experimental and clinical studies of Lehman, Borg, Batterman, Herrmann and their associates, who found that the subcutaneous injections of Thiomerin were safe and free from local reactions.[7, 9, 10, 19]

More than 90 per cent of the patients suffering from edema of cardiac, renal, and hepatic origin responded satisfactorily to subcutaneous Thiomerin. A comparative study made with Mercuzanthin given intramuscularly showed that the rate of onset, the peak, and the duration of diuresis following equivalent amounts of the two mercurials in the same individual were approximately the same. Borg and Craig stated that "systemic reactions due to excessive diuresis are more frequently seen after Thiomerin administration than after intravenous injections of other mercurials."[9] This was not the impression obtained from this study as compared with previous clinical experience using mercurial diuretics intravenously.

Symptoms of dehydration and electrolyte imbalance as reported by Poll, Ben-Asher, DeGraff and others[11, 12, 13, 14] were seen in seven patients of this series. All of these patients were receiving 2 c.c. of Thiomerin daily and had a profuse diuresis as indicated by rapid weight loss. After a brief period of interruption of the drug, 1 c.c. doses were utilized at less frequent intervals. With this modification of dosage, there was no recurrence of the syndrome of salt depletion. Three patients, receiving only 0.5 c.c. of Thiomerin daily, did not show appreciable weight loss for three days. Diuresis began soon after larger doses of the drug were employed. These observations would tend to indicate that in the majority of patients, satisfactory but not excessive diuretic response can usually be obtained by 1 c.c. of Thiomerin at daily or less frequent intervals.

It must be stressed that mercurial diuretics may do harm in patients suffering from severe renal disease with nitrogen retention.[20] Thiomerin administration may have been a contributory factor in the rapidly rising blood urea nitrogen in two patients with chronic renal lesions, uremia, and massive edema. Pharmacologically, Keith, Sollmann and others have shown that the diuretic effect of all the organic and inorganic mercurials is dependent upon the free mercury ions which are released from the compound by the tissues and body fluids.[15, 16] It is also known that these free mercury ions exert a mild toxic effect on the renal tubules producing the desired clinical effect.[17, 18] Since it has been shown that the diuretic action of Thiomerin is the same as other organic mercury compounds, it is reasonable to believe that its pharmacologic action is also dependent on the dissociated free mercury ions. One should therefore caution against the use of Thiomerin in cases with severe kidney disease, and especially in those patients who show marked impairment of renal function.

Lehman has demonstrated that moderate doses of Thiomerin can be administered intravenously to experimental animals with only minimal toxic effects to the heart.[8] In clinical use, however, subcutaneous Thiomerin has been found to be practically free from irritation. The intravenous route of administration, with its possible attending cardio-toxic effects, can therefore be avoided.

Summary

1. A new organic mercurial diuretic (Thiomerin) was administered by the subcutaneous route to 111 patients suffering from edema due to cardiac, hepatic, and renal diseases.

2. The range of dosage was from 0.5 c.c. to 2 c.c. This was given daily, or from every second to fourth day. The majority of patients received 1 c.c. or 2 c.c. of the drug daily for six to 10 days.

3. The onset of diuresis was noted in the first 24 hours of treatment in 78 of the 106 hospitalized patients.

4. Some diuretic effect was usually demonstrable for about two days after the injection.

5. A comparative study made with Mercuzanthin solution administered intramuscularly revealed that the diuretic action of these two preparations was quantitatively similar.

6. There were seven instances of local pain or burning following 891 subcutaneous injections of Thiomerin. Three patients developed minor local lesions at the site of injection.

7. Seven patients developed salt depletion syndrome following profuse diuresis from mercurial therapy.

8. More than 90 per cent of 111 patients with edema responded satisfactorily to the subcutaneous mercurial diuretic.

BIBLIOGRAPHY

1. Higgins, W. H.: Acute toxic effects of mercurial diuretics, J. A. M. A. **119**: 1182, 1942.
2. DeGraff, A. C., and Nadler, J. E.: A review of the toxic manifestations of mercurial diuretics, J. A. M. A. **119**: 1006, 1942.
3. Wexler, J., and Ellis, L. B.: Toxic reactions to intravenous injections of mercurial diuretics, Am. Heart J. **27**: 86, 1944.
4. Pines, I., Sanabria, A., and Hernandez Arriens, R. T.: Mercurial diuretics; addition of magnesium sulfate to prevent toxic effects of their intravenous administration, Brit. Heart J. **6**: 197, 1944.
5. Kauffman, R. E.: Immediate fatalities after intravenous mercurial diuretics, Ann. Int. Med. **28**: 1040, 1948.
6. Oettlé, A. G.: Sudden death after intravenous injection of a mercurial diuretic, Brit. M. J. **2**: 530, 1947.
7. Lehman, R. A., Taube, H., and King, E. E.: A comparative study of the local toxic action of mercurial diuretics. To be published.
8. Lehman, R. A.: Further studies on the acute toxicity of mercurial diuretics, Proc. Soc. Exper. Biol. and Med. **64**: 428, 1947.
9. Borg, J. F., and Craig, D. M.: Experiences with a mercurial diuretic for subcutaneous injection, Proc. Central Soc. Clin. Res. **21**: 82, 1948.
10. Batterman, R. C., Utterman, D., and DeGraff, A. C.: The subcutaneous use of Thiomerin, a new mercurial diuretic for treatment of congestive heart failure. To be published.
11. Poll, D., and Stein, J. E.: Untoward effects of diuresis, Arch. Int. Med. **58**: 1087, 1936.
12. Ben-Asher, S.: On the toxicity of the mercurial diuretics: observations on 18 cases with suggestions for prevention of toxic reactions, Ann. Int. Med. **25**: 711, 1946.
13. Marshall, F. A.: Tetany following mercurial diuresis, J. A. M. A. **133**: 1007, 1947.
14. DeGraff, A. C.: Diuretics, J. A. M. A. **136**: 1025, 1947.
15. Keith, N. M.: The pharmacopoeia and the physician; action and use of diuretics, with special reference to mercurial compounds, J. A. M. A. **107**: 2047, 1936.
16. Sollmann, T., and Schreiber, N. E.: The diuretic effects of various mercurial treatments, Am. J. Physiol. **93**: 689, 1930.
17. Bartram, E. A.: Experimental observations on effect of various diuretics when injected directly into the renal artery of dog, J. Clin. Investigation **11**: 1197, 1932.
18. Christian, H. A., and Bartram, E. A.: Experimental observations on the action of diuretics, Trans. Ass. Am. Physicians **47**: 292, 1932.
19. Herrmann, G. R.: Myocardial insufficiency; mechanism and management with data on a new and safer mercurial diuretic, J. A. M. A. **140**: 509, 1949.
20. Kline, E. M., and Seymour, W. B.: Systemic reactions to mercurial diuretics, Am. J. M. Sc. **203**: 874, 1942.

STUDIES RELATIVE TO THE CHEMOTHERAPY OF BACTERIAL ENDOCARDITIS *

By M. H. NATHANSON, M.D., F.A.C.P., and RUTH A. LIEBHOLD,
Los Angeles, California

THE introduction of a successful therapeutic agent in a disease often leads to clarification of the nature of that disease. This is illustrated by the progress that has been made in the elucidation of the nature of diabetes mellitus since the advent of insulin, and the similar progress in the understanding of various diseases of the blood following the introduction of liver therapy.

In the case of subacute bacterial endocarditis, the uniformly fatal character of the disease prior to the use of penicillin and the failure of various therapeutic agents have not been adequately explained. The low virulence of the usual infecting organism, the alpha hemolytic streptococcus (*viridans*), suggests that the severity of the disease has more to do with peculiar reactions of the host than with any inherent pathogenicity of the organism. There is convincing evidence that there is no defect in the systemic defense of the host, indicating that the persistence of the disease is dependent upon the local reaction on the valve, which permits the survival of the infecting organism in this locus. In support of such a concept, the following may be mentioned: therapeutic agents, including the sulfonamides, may clear the blood stream of the infecting organism. At autopsy, in spite of high levels of the antibacterial substance in the blood, the vegetations can be found to contain many viable organisms. Also, in bacterial endarteritis such as occurs in association with a patent ductus arteriosus, or an arteriovenous aneurysm, chemotherapeutic agents have been consistently ineffective. However, surgical elimination of the infected thrombotic lesion is usually followed by a rapid disappearance of the bacteria from the blood stream and cure of the disease. These observations suggest that the disease persists because natural defense mechanisms and antibacterial agents are unable to inhibit the multiplication of bacteria in the thrombotic lesion.

The organisms in the vegetation are separated from the blood stream by a layer of fibrin, and it has been shown that many antibacterial agents penetrate fibrin poorly or not at all. Friedman [1] studied the effects of three germicides: gentian violet, merthiolate, and Vuzino-toxine camphorated on *Streptococcus viridans* embedded in a fibrin mass. He compared the effect with that occurring in ordinary broth cultures of the same organism and

* Received for publication October 14, 1948.
From the University of Southern California, School of Medicine; and Research Laboratories, Cedars of Lebanon Hospital.
This study has been carried out with the support of the Dorothy H. and Lewis Rosenstiel Foundation.

found that the fibrin had a striking retarding effect on the bactericidal action of these compounds. Friedman [2] also demonstrated that sulfanilamide and sulfapyridine failed to eradicate a focus of streptococci growing in a fibrin-platelet mass. Duncan and Faulkner [3] were unable to demonstrate any appreciable penetration of sulfonamide compounds into blood clots in periods of from 24 hours to 15 days. These studies suggest that failure of therapy in bacterial endocarditis may be due to an inhibiting or retarding effect of fibrin on antibacterial agents.

The purpose of the present study was to determine the influence of fibrin on the antibacterial activity of several bactericidal agents, and is an extension of previously reported work.

Procedure: A modification of the cup assay method for penicillin was utilized. Agar plates were prepared with *Bacillus subtilis* as the test organism, in accordance with the technic of Foster and Woodruff.[5] Fibrin plates were prepared in the following manner: dried fraction I * of human plasma was reconstituted by the addition of saline containing 10 per cent glucose. Twenty c.c. portions were poured into petri dishes and 0.2 c.c. of a spore suspension of *B. subtilis* was added to each plate.

TABLE I

	Diameter of Zones of Inhibition in mm.			
	M/25 Sodium-Sulfathiazole		M/25 Sodium-Sulfadiazine	
	Agar	Fibrin	Agar	Fibrin
24 hours	0	0	0	0
48 hours	12	0	0	0
72 hours	15	0	14	0
96 hours	18	0	18	0

The plates were shaken to permit an even distribution of the bacterial suspension. To each plate 0.2 c.c. of a solution of bovine thrombin was added, prepared by dissolving 5,000 units in 5 c.c. of isotonic saline. The fibrin hardened within two minutes after the addition of the thrombin. Three penicillin assay cups were placed equidistant from one another on each agar and fibrin plate. The three cups were filled with the substance to be tested, which permitted the reading of the results in triplicate. The plates were kept at room temperature because preliminary experiments showed that liquefaction occurred in the fibrin at incubator temperature. Measurements of the diameter of the zones of inhibition were made at 24 hour intervals.

* This plasma fraction was prepared under a contract between the Office of Scientific Research and Development and Harvard University, from blood collected by the American Red Cross. This was supplied by the Department of Physical Chemistry, Harvard Medical School. In this fraction, 60 per cent of the protein is fibrinogen and the remainder is albumin and globulin.

Sodium sulfathiazole and sodium sulfadiazine in M/25 solutions were used to determine the antibacterial activity of the sulfonamides in agar and in fibrin. Table 1 represents the data in one experiment and illustrates the inactivity of these compounds in fibrin. A number of experiments were carried out with varying concentrations of penicillin. Table 2 shows the results of a typical experiment. These studies indicate a striking difference in the antibacterial activity in fibrin between the sulfonamides and penicillin. As compared with the inactivity of the sulfonamides, penicillin appears to possess an uninhibited activity in fibrin.

Two explanations may be considered for the failure of sulfonamides to show antibacterial activity in fibrin: (1) inability of sulfonamides to penetrate fibrin, and (2) inactivation of sulfonamides by fibrin. Applied to the endocarditic lesion, sulfonamides might be ineffective because of failure to penetrate the vegetation or because of their inactivation by the fibrin content of the lesion. The following experiments were carried out to determine whether fibrin had an inhibiting action on sulfonamides: M/25 aqueous

TABLE II

Penicillin units/c.c.	Diameter of Zones of Inhibition in mm.					
	0.5		1.0		2.0	
	Agar	Fibrin	Agar	Fibrin	Agar	Fibrin
24 hours	9	9	9	9	11	9
48 hours	10	9	11	9	12	9.5
72 hours	11	9	12	10	12	10
96 hours	12	10	13	12	14	13

solutions of sodium sulfathiazole and sodium sulfadiazine were prepared. Similar concentrations of the sulfonamides were prepared with fraction I of human plasma as the diluent. In this plasma fraction, 60 per cent of the protein is fibrinogen. The aqueous and plasma solutions were poured into assay cups and placed on agar plates seeded with *B. subtilis*. The plates were incubated at 37° C. and the zones of inhibition measured at 24 hour intervals. Three cups were used for each preparation and the average of the three readings was taken. Examination of the plates for periods up to 96 hours showed that there was no significant difference in size of the inhibition zones produced by the aqueous and plasma solutions of the sulfonamides. These experiments indicate that the presence of fibrinogen does not influence the antibacterial activity of the sulfonamides studied. The following procedure was also used to determine the influence of fibrin on the activity of the sulfonamides: Assay cups placed on seeded agar plates were filled with M/25 aqueous solutions of sodium sulfathiazole and sodium sulfadiazine. Eight plates were prepared for each compound. To the assay

cups on four plates were added varying amounts of fibrin particles. The remaining plates containing the untreated sulfonamide compounds served as controls. The plates were incubated at 37° C. and readings of the inhibition zones were made at 24 hour intervals. There was no significant difference in the size of the inhibition zones in the plates containing the sulfonamides and fibrin as compared with the controls. These experiments failed to demonstrate any inhibiting effect of fibrinogen or fibrin on the sulfonamides, and indicated that the inactivity of these compounds in fibrin is due to their inability to penetrate fibrin.

In support of these in vitro experiments, the following clinical study demonstrates the diffusion of penicillin into an endocardial vegetation in a case of subacute bacterial endocarditis.

Case Report

The patient was a woman, aged 35, who gave a history of general body pains, fever, and weakness of seven months' duration. Shortly after the onset of her illness she was seen by a physician who suspected subacute bacterial endocarditis, and *Streptococcus viridans* was repeatedly recovered from the blood. She received increasing doses of penicillin, with only temporary improvement and sterilization of the blood stream for short periods. In spite of therapy the fever persisted and there was increasing anemia and weight loss. Three weeks before admission to the hospital, she developed increasing edema of the lower extremities.

Examination on admission to the hospital on September 7, 1946, revealed that she was in a moderate stupor. Extreme emaciation was present and there was marked pallor of the skin and mucous membranes. The heart was enlarged to the left, the rate was 100, and a loud systolic murmur was heard over the cardiac apex. There were fine moist râles at the bases of both lungs. The spleen was slightly enlarged. There was a marked edema of both lower extremities. The blood nonprotein nitrogen was 95 mg. and the creatinine 4.5 mg. The patient became comatose and died two days after admission to the hospital. During her hospital stay, she received 200,000 units of penicillin every six hours intramuscularly. The last dose was administered two hours before death.

Necropsy report: The chief extracardiac finding was a renal lesion which was diagnosed as nephrosis. The cardiac findings were the following: The heart weight was 440 gm. Covering the mitral cusps were large, light yellow, friable vegetations which projected into the left auricle (figure 1). The vegetations measured up to 2.5 cm. in height and were firmly fixed to the valve leaflets. The tricuspid valve showed several smaller vegetations. On microscopic examination, the endocardium was thickened in many places. The mitral valve leaflets, aside from the vegetation, appeared thickened and vascularized, apparently due to old rheumatic scarring. The vegetation showed some evidence of organization, and the endocardium covered the vegetations in many sections. Aside from the evidence of organization, the vegetations consisted chiefly of fairly well preserved fibrin, enmeshed in which were numerous leukocytes and clumps of bacteria. A gram stain showed these bacteria to be gram positive cocci. A considerable amount of necrotic debris was also found within the core of the vegetation.

At the postmortem examination, fragments of approximately equal size were removed from the surface of the largest vegetation and from the deepest part after

removal of the surface layer. A small fragment of spleen was also removed. These fragments were immediately placed on an agar plate seeded with *B. subtilis* and incubation carried out for 24 hours. Figure 2 shows the inhibition zones surrounding the tisssue fragments at this time. There is a definite zone of inhibition surrounding

FIG. 1. Large vegetations on the mitral valve from which fragments were removed for assay for penicillin.

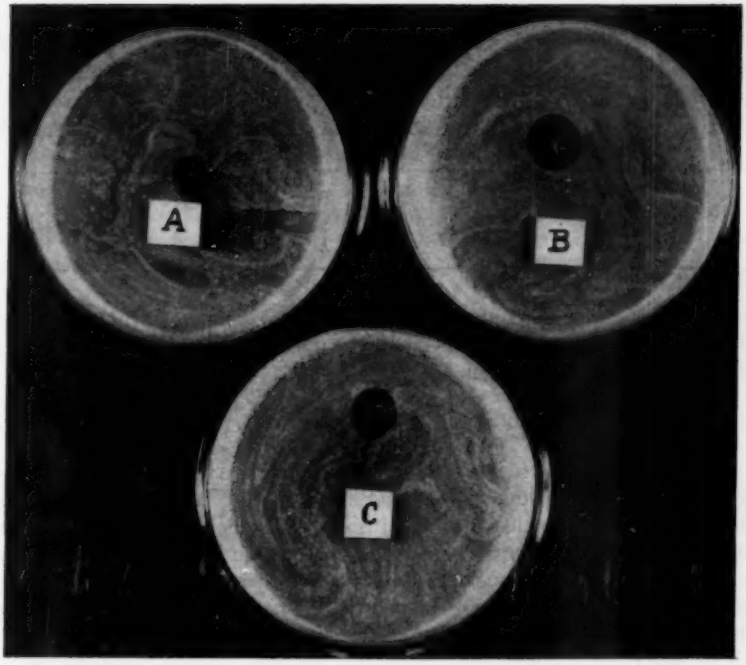


FIG. 2. Agar plates seeded with *B. subtilis*. A—Inhibition zone surrounding fragment of spleen; B—Inhibition zone surrounding tissue removed from surface of vegetation; and C—Inhibition zone surrounding tissue removed from deep portion of the vegetation.

the fragment removed from the deep portion of the vegetation, indicating that penicillin had penetrated into the vegetation.

It seemed of importance to determine the activity of streptomycin in fibrin, since in certain circumstances this antibiotic must be considered in the therapy of bacterial endocarditis. Streptomycin would be indicated in the occasional case in which the causative organism is a streptomycin-sensitive gram-negative bacillus. This antibiotic would also receive consideration in cases due to the nonhemolytic streptococcus in which the organism is resistant to penicillin. It has been shown that such organisms are occasionally relatively sensitive to streptomycin.[6]

The procedure described in the study of the activity of penicillin in fibrin was followed. Aqueous solutions of streptomycin in concentrations of 25 and 50 units (micrograms) per c.c. were placed in assay cups on seeded agar and fibrin plates. Measurements of the zones of inhibition were made at 24 hour intervals. The results of these experiments are shown in table 3. There is some delay in the appearance of inhibition in the fibrin as compared with the agar, and the zones are slightly larger in the agar. However, these

TABLE III

	Diameter of Zones of Inhibition in mm. Streptomycin, mcgm./c.c.			
	25		50	
	Agar	Fibrin	Agar	Fibrin
24 hours	12	0	15	0
48 hours	13	10	17	13
72 hours	14	10	18	14
96 hours	15	12	20	16

experiments show a definite activity of streptomycin in fibrin and indicate that this antibiotic should be effective in bacterial endocarditis due to a streptomycin sensitive organism.

COMMENT

It is realized that in vitro experiments may not be strictly applicable to disease in the living patient. However, the following facts appear to be established and certain conclusions seem justifiable: Penicillin and, more recently, streptomycin have shown a remarkable therapeutic effectiveness in bacterial endocarditis. All previously used antibacterial agents, including the sulfonamides, have been relatively ineffective. The present experiments show that penicillin and streptomycin penetrate and show antibacterial activity in fibrin, while the sulfonamides fail in this respect. These observations support the concept of a fibrin barrier on the valve which protects the organisms from harmful agents, and therefore permits the persistence of the infection on the valve. It follows that in the consideration of the possible value of any therapeutic agent for bacterial endocarditis, an essential property should be its ability to penetrate and show antibacterial activity in fibrin.

A further implication of this study relates to the use of anticoagulants in the treatment of subacute bacterial endocarditis. Heparin has been used as an adjunct to antibacterial agents with the purpose of lessening the deposition of fibrin and rendering the bacteria more accessible. Although some clinical reports suggest that heparin is beneficial, others indicate that the results are not improved by its use. The present experiments would tend to minimize the importance of heparin, since fibrin appears to have no retarding effect on the activity of penicillin and streptomycin.

CONCLUSIONS

Penicillin and streptomycin exhibit antibacterial activity in fibrin, while sodium sulfathiazole and sodium sulfadiazine are ineffective.

The inactivity of the sulfonamides is not due to inactivation of the drug but is the result of its failure to diffuse into fibrin.

The indication is that the therapeutic efficiency of a compound in bacterial endocarditis depends on its ability to penetrate fibrin.

These observations suggest that the persistence of the infection on the valve is the result of a fibrin barrier which protects the infecting organisms from antibacterial agents.

BIBLIOGRAPHY

1. Friedman, M.: A study of the fibrin factor in its relation to subacute endocarditis, J. Pharmacol. and Exper. Therap. **63**: 173, 1938.
2. Friedman, M.: Use of sulfanilamide and sulfapyridine in therapy of subacute bacterial endocarditis, Arch. Int. Med. **67**: 921, 1941.
3. Duncan, C. N., and Faulkner, J. M.: Penetration of blood clot by sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole, Am. J. M. Sc. **200**: 492, 1940.
4. Nathanson, M. H., and Liebhold, R. A.: Diffusion of sulfonamides and penicillin into fibrin, Proc. Soc. Exper. Biol. and Med. **62**: 83, 1946.
5. Foster, J. W., and Woodruff, H. B.: Microbiological aspects of penicillin, J. Bact. **47**: 43, 1944.
6. Priest, W. S., and McGee, C. J.: Streptomycin in the treatment of subacute bacterial endocarditis, J. A. M. A. **132**: 124, 1946.

THE EFFECTS OF VARIOUS PHYSICAL PROCEDURES ON THE CIRCULATION IN HUMAN LIMBS *

By Robert W. Wilkins, M.D., Meyer H. Halperin, M.D., and Julius Litter, M.D., *Boston, Massachusetts*

During the past 10 years a series of physiologic studies has been carried out on the effects of various physical procedures upon the circulation in the limbs, in the hope of obtaining information of practical value in the physical therapy of peripheral vascular diseases. The purpose of the present paper is to review and summarize this work in order that clinical implications may be more easily derived. The physical procedures that have been studied may be grouped under three main headings: (1) heat; (2) posture, and (3) pressure cuffs.

Heat

Heat is a well-known vasodilator and its effects are striking, whether it is applied generally to the body or locally to a part of a limb. However, there is a distinct difference in the physiologic mechanism of vasodilatation produced by general body heating and that produced by direct local heating. The first involves widespread activity of the sympathetic nervous system, while the second may involve vasodilation only in the local tissues being heated.

When a normal subject is placed unclothed in a room at about 20° to 22° C. (68° to 72° F.) and measurements are made of the skin temperature of a fingertip, and of the blood flow (plethysmographic) in an adjacent finger, one finds that the temperature usually comes to rest at 20° to 30° C. and the blood flow at 0.1 c.c. to 0.5 c.c. per finger (of about 10 c.c. volume) per minute (figures 1, 7).[1] If one then warms the subject by applying heating pads and blankets to his body, or by putting his feet and legs into a hot tub, the finger temperature rises rapidly to about 36° C. and the blood flow to 5 c.c. to 10 c.c. per minute. Cooling the body by removing the heating pads and blankets, or by putting the feet and legs into cool water, then causes the finger temperature and blood flow to fall. The drop in finger temperature lags behind the decrease in blood flow because of the latent heat of the tissues which, once warmed, cool slowly even when blood flow is cut off completely, as with a tourniquet. It is well known that these changes in temperature and blood flow in the hands and feet are reflex in

* Presented at the Thirty-First Annual Session of the American College of Physicians, Boston, Mass., April 21, 1950.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

nature and do not occur in a sympathectomized limb, which maintains a relatively constant, neutral state of mid-vasodilatation.

When, in a similar experiment on a normal subject, a single finger is heated in a special water-jacketed plethysmograph, there is no effect on body temperature or on the blood flow in the remaining fingers.[1] In this way the vasodilating effect of local heat alone may be studied with the body cool. The blood flow in the finger is markedly increased by local heating, but is still not so great as when the body alone is heated. Furthermore, with the

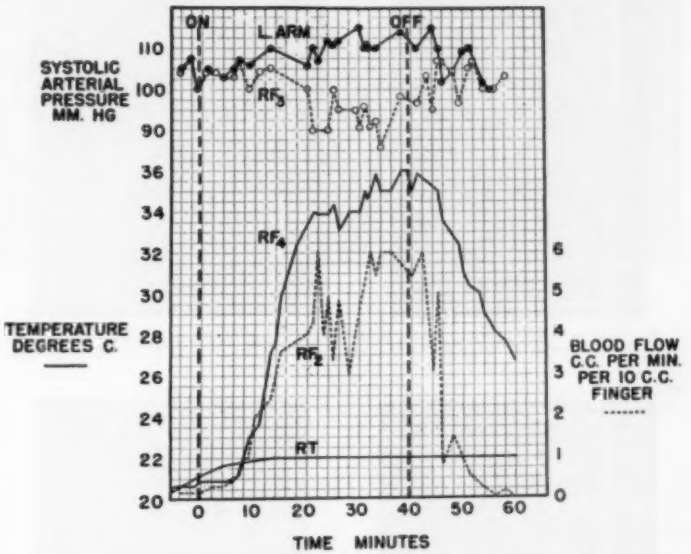


FIG. 1. Chart of systolic arterial pressure in the left upper arm (solid dots and lines), and in the right middle finger (circles and interrupted lines); of the temperature of the right ring finger (RF_4), and of the room (RT), and of blood flow in the right forefinger (RF_2). At "On" the subject was covered with blankets and his legs were placed in water at 45° C.; at "Off" he was uncovered and his legs were removed from the hot water. In the middle of the test, when the body was warm, the skin temperature and blood flow in the fingers were increased, and the arterial pressure in the finger was 20 to 30 mm. Hg lower than that in the arm.

body already heated, the blood flow in the finger does not become much greater when the finger is also heated locally. Thus, the reflex vasodilating effect of heating the body upon blood flow in the fingers appears to be more important than that of local heating alone. Conversely, the effects of sympathetic nervous vasoconstriction may be important in reducing the blood flow in the extremities even when they are heated locally to the limits of tolerance of the subject. This may be shown directly by applying a reflex vasoconstrictor stimulus, such as ice, to a remote part of a subject

while the blood flow is being measured to one finger with, and to another without, local heating. The blood flow in both fingers definitely is reduced, although to a lesser degree in the heated finger.

Similar experiments may be done on the muscular parts of the limbs, for example, the forearm or calf.[2] When plethysmographic measurements of blood flow are made on the two forearms of a subject lying in a cool room, they vary between 2 and 3 c.c. per 100 c.c. of limb per minute and are nearly

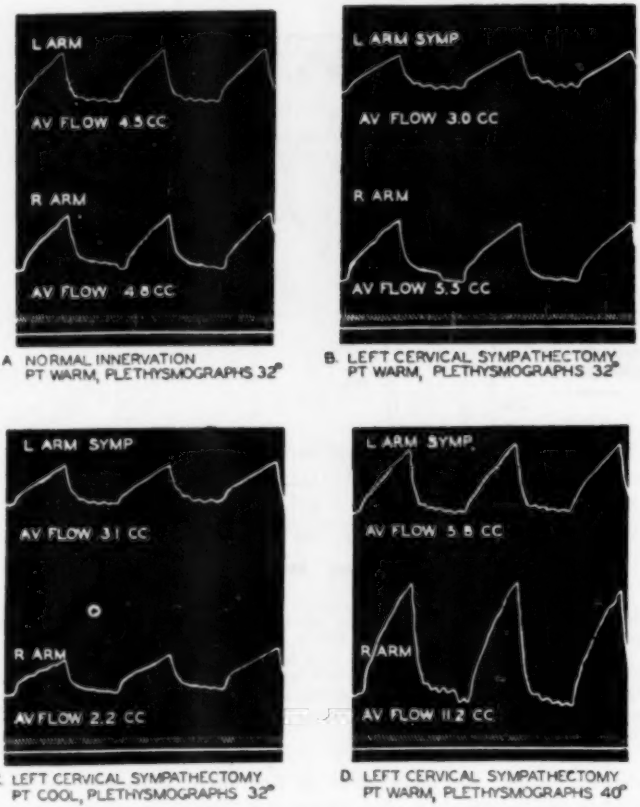


FIG. 2. Plethysmographic tracing of blood flow to the forearms of a patient with Raynaud's disease of the hands. Each set of determinations represents a different experiment as noted: A, before operation; B, C, and D, fourteen days after left cervical preganglionic sympathectomy. The calculated average blood flow in c.c./100 c.c. of arm/min. is given under each set of tracings. The blood flow was equal in the two arms when normally innervated (A). After unilateral sympathectomy the blood flow in the denervated arm failed to increase or decrease with warming or cooling of the body, but remained at a constant neutral level (B, C). With local heating the blood flow increased in both the normal and the denervated arm (D).

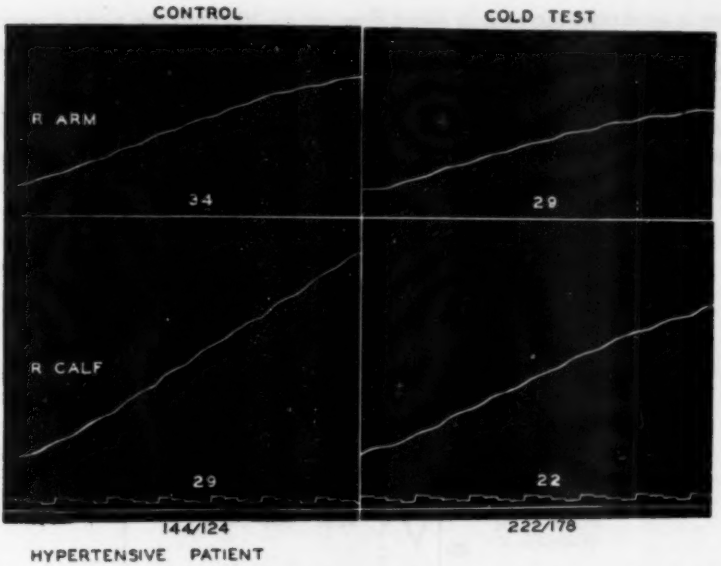


FIG. 3. Plethysmographic tracings of reactive hyperemia blood flow to the right forearm and calf of a hypersensitive patient. The tracings on the left were obtained during the control period, those on the right during the immersion of the left hand in iced water (Cold Test). The calculated blood flow in c.c./100 c.c. of limb/min. is given under each tracing. During the cold test the flow decreased markedly in both limbs despite a considerable increase in arterial pressure.

equal in the two arms. After the body is warmed with heating pads and blankets, the flows increase equally to 4 to 5 c.c. per 100 c.c. per minute (figure 2). After a unilateral cervical sympathectomy, when the subject is uncovered in a *cool* room, the blood flow in the sympathectomized arm is greater than in the normally innervated arm. However, since the blood flow in the sympathectomized arm does not change appreciably with body warming, it is surpassed by the blood flow in the normal arm when heating pads and blankets are applied to the body (figure 2). Furthermore, when the arms are now heated locally by warming the water in the plethysmographs, the blood flow increases in both but is considerably greater in the normally innervated than in the sympathectomized arm. Thus, blood flow in the muscular parts of the limbs is influenced reflexly by body heating and cooling in qualitatively the same way, but in quantitatively a smaller degree than the blood flow in the hands and feet. A much more complete vasodilatation may be produced in the muscular parts of the extremities by "reactive hyperemia" than by either general or local heating, or both.[3] This is done by first causing absolute or relative ischemia, with occluding or obstructing cuffs placed proximally on the part. On release of the obstruction,

there is a marked increase in blood flow, up to 10 times the control resting levels. However, even this degree of vasodilatation may be partially overcome by very strong or painful reflex vasoconstrictor stimuli (figure 3).

It is of theoretical interest, and perhaps of clinical importance, that such changes in the circulation in the limbs definitely affect the level of the arterial pressure in the distal parts of the extremities, particularly in the digits.[4] Thus, systolic arterial pressures taken simultaneously in a finger of one hand

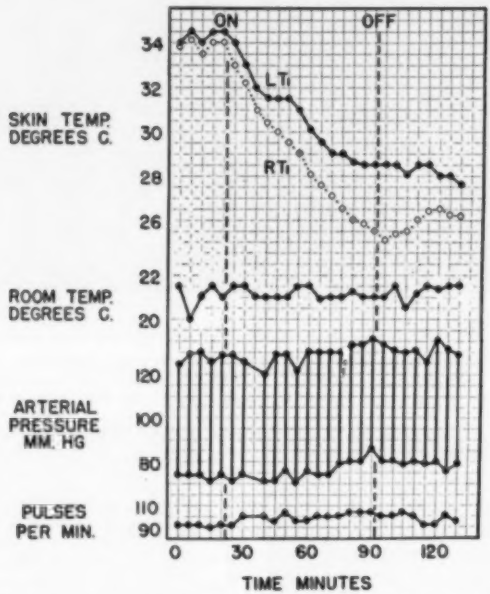


FIG. 4. Chart of skin temperature of the left great toe (LT_1) and of the right great toe (RT_1), room temperature, arterial pressure, and pulse rate during an experiment on a normal subject. Throughout the experiment the subject was warmed by blankets and electric heating pads. At 22 minutes (first vertical interrupted line) both feet were raised 75 cm. above the bed, and a cuff above the right knee was inflated to 50 mm. Hg. At 92 minutes, the cuff was released. During elevation both feet cooled, but the congested foot cooled more rapidly, suggesting that it had a lower blood flow than the control.

and in the opposite arm are found to be nearly equal when the subject is cool. When the subject is warmed, however, the pressure is 20 to 30 mm. Hg lower in the finger than in the arm (figure 1). During a brief reflex vasoconstrictor response in the hand the pressure in the finger rises toward that in the arm and falls again with the ensuing vasodilatation. That the lowering of pressure in the finger is due to a side loss of pressure through the widely dilated peripheral arteries may be shown by occluding with small cuffs the arteries to the other four fingers of the hand, whereupon the systolic

pressure in the remaining finger rises towards that in the arm. In a similar way, arterial pressure in one foot is lowered below that in the opposite foot if marked vasodilatation is produced in the calf above it by muscular exercise or reactive hyperemia.[4] This demonstrates that pressure in a distal artery may be dissipated by vasodilatation in more proximal or in side branches which in this way might deprive peripheral areas of blood flow. This effect may be of great importance beyond an obstruction in a diseased peripheral artery where the available head of pressure is already reduced, and therefore is the critical factor determining blood flow even when there is considerable vasodilatation distally.

Posture

Arterial pressure, or rather the arteriovenous pressure gradient, is the force that drives the blood against the peripheral vascular resistance and

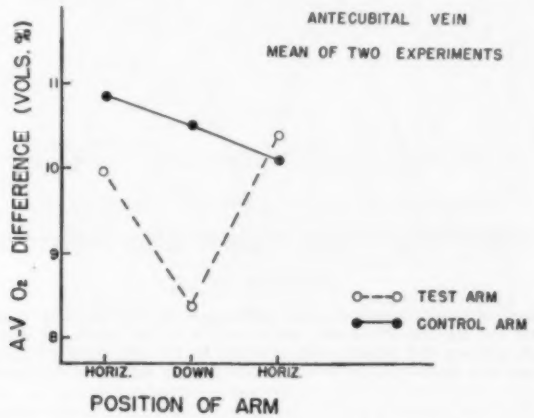


Fig. 5. Chart of the mean arteriovenous oxygen differences in the arms during two experiments on normal subjects. At first both arms were horizontal and on a level with the heart. Then the "test arm" was lowered into a dependent position. Finally it was returned to the control position. The decrease in arteriovenous oxygen differences during dependency was interpreted as an increase in blood flow.

(if resistance is constant) determines the blood flow. Blood pressure in peripheral arteries, as we have just seen, may be affected independently of that in central or "systemic" arteries. One of the simplest and most common means by which it may be so affected is through the hydrostatic effects of changes in posture. Thus, it is well known that elevating the limbs above heart level lowers the arterial pressure in them without greatly affecting venous pressure, thereby decreasing the arteriovenous pressure gradient, and reducing the blood flow (and skin temperature) in them

(figure 4). It is also obvious that lowering the limbs below heart level increases the arterial pressure in them by the hydrostatic distance that they are lowered. Since the venous pressure rises to an equal degree when the veins are distended by arterial inflow, the arteriovenous pressure gradient is restored, and one might assume that the blood flow returns to previous (horizontal) values. However, a not infrequent clinical observation is that certain patients with marked ischemic peripheral arterial disease prefer to keep their limbs, at least intermittently, in a dependent position. For this reason, a study was done to see if the blood flow was less, the same, or greater in a limb when dependent than when horizontal.[5] Using the arteriovenous oxygen differences as a measure of blood flow, it was found in

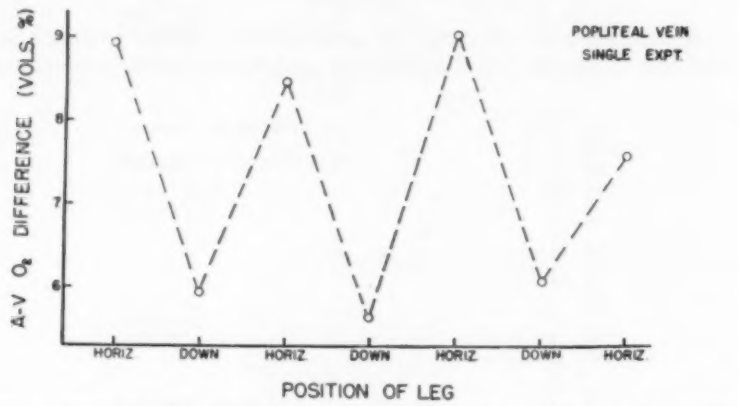


FIG. 6. Chart of arteriovenous oxygen differences in the popliteal vein of a normal subject. At first the leg was horizontal, on a level with the heart. It was then lowered into a dependent position and subsequently returned to the horizontal position, three times. Whenever the leg was dependent the arteriovenous oxygen difference decreased (blood flow increased).

both the arm and the leg that the A–V oxygen difference was less, and therefore the flow was greater, when the limb was dependent than when horizontal (figures 5, 6). Venous pressure measured locally was found to be increased by the hydrostatic distance that the limb had been lowered. The reason advanced for the greater blood flow in a dependent limb was that the peripheral resistance is lowered by passive distention (dilatation) of the arterioles and minute vessels by the hydrostatic increase in local intravascular pressure.

PRESSURE CUFFS

Certain workers had hoped to utilize the principle just mentioned, namely, passive distention of the peripheral blood vessels to lower the peripheral resistance, by means of blood pressure cuffs applied proximally on

the limb to produce peripheral venous distention. However, they failed to realize that such a method does *not* leave the arteriovenous pressure gradient unchanged, but decreases it by the amount of the venous congesting pressure used. Nevertheless, the method has been advocated for therapy clinically, and experiments in animals have been cited as evidence in support of it. Therefore, an extensive study was done in man to determine whether such "venous occlusion" enhances, impedes, or does not affect peripheral blood flow in the limbs.[6]

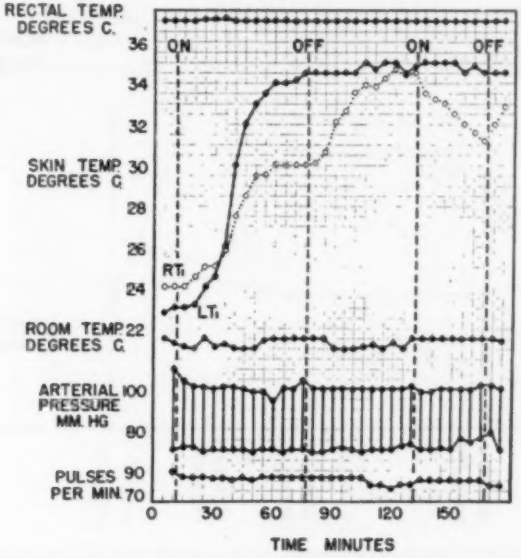


FIG. 7. Chart of rectal temperature, skin temperature of the right great toe (RT_1), and of the left great toe (LT_1), room temperature, arterial pressure, and pulse rate during an experiment on a normal subject. At the beginning of the experiment the subject was covered with blankets and electric heating pads. At 12 minutes (first vertical interrupted line) a cuff above the right knee was inflated to 50 mm. Hg. At 77 minutes (second vertical interrupted line) the cuff was released; at 132 minutes it was re-inflated, and, at 168 minutes, released. During body warming, the skin temperature of both feet increased, but less in the congested than in the control limb, suggesting that it had the lower blood flow.

When a cuff is inflated at 50 mm. Hg proximally on one limb of a normal subject in a cool room, and at the same time blankets and heating pads are placed on the body, the digits of that limb do not warm as quickly or as much as those of the opposite side (figure 7). Release of the congesting cuff then allows the digits to warm to the level of the controls, whereas re-inflation of the cuff causes the congested digits to cool again. Contrariwise, when a cuff is inflated at 50 mm. Hg proximally around the limb of a subject already warmed, and at the same time the heating pads and blankets are

removed from his body, the digits on that side cool more rapidly than the ones on the uncongested side. Similarly, venous congestion of one limb accelerates the normal cooling of the foot caused by elevating the limb above heart level (figure 4). Furthermore, venous congestion of a limb decreases the oxygen content of the venous blood (increases the A–V oxygen difference) in that limb. Finally, plethysmographic measurements of blood flow in a limb during (as compared with before and after) venous congestion show a decrease in blood flow during congestion.[6]

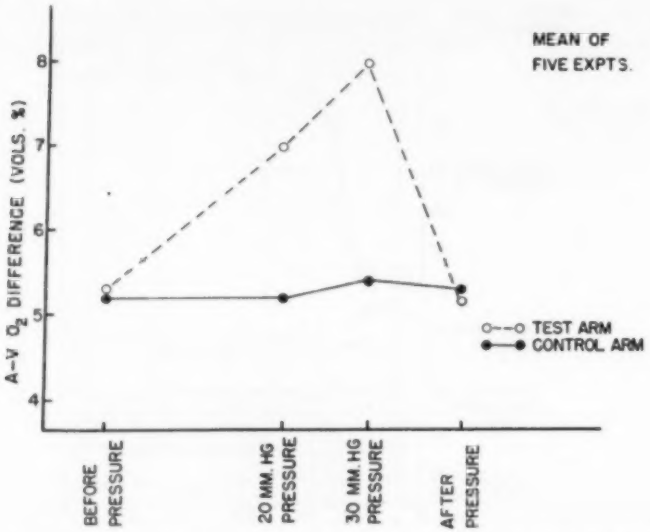


FIG. 8. Chart of mean arteriovenous oxygen differences in the arms of five normal subjects, showing the effect of local pressure. During the application of pressure an increase in the arteriovenous oxygen difference occurred in the "test arm" indicating a decrease in blood flow. The contralateral control arm showed no change.

It seemed important to know also what effect pressure as from a cuff would have on the blood flow locally in the pressurized part, directly under the cuff.[7] With measurement of skin temperature, which was the least sensitive method used to estimate blood flow, it was possible to show that pressures of 30 mm. Hg applied locally on the hand reduced the flow. With measurement of the A–V oxygen difference as an index, 20 as well as 30 mm. Hg local pressure uniformly caused a decrease in blood flow in the forearm (figure 8). However, with very careful plethysmographic methods it was possible to demonstrate that local pressure of as little as 10 mm. Hg produced a 10 per cent decline in blood flow. Furthermore, when the plethysmographic values were plotted in comparison with the oxygen data against pressure, very similar curves were obtained suggesting that blood

flow is reduced in direct proportion to the amount of pressure applied on a part even at less than 20 mm. Hg (figure 9).

Realizing the facts just cited, it was of great interest to observe that local compression of a limb at 10 to 30 mm. Hg definitely accelerated the linear velocity of blood flow in the *veins* in that limb.[8] This was demonstrated by measuring the progress of a small dose of a radio-opaque substance (diodrast) or of a colored dye (T–1824) injected into a distal vein before, during, and after local compression of the limb. The measurements indicated a 20 to 150 per cent increase in linear velocity in the venous flow during compression. They were confirmed by the results of venous circulation times (decholin) done under similar conditions. There seems little doubt that mild local compression (at about 20 mm. Hg) increases the linear

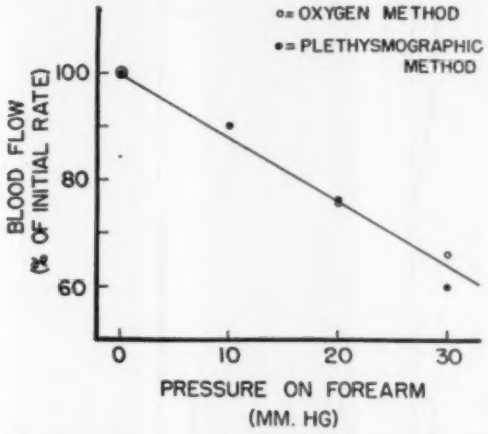


FIG. 9. Chart comparing the decrease in blood flow in the forearm of a normal subject as measured by arteriovenous oxygen differences, and by plethysmographic methods during the local application of pressure as indicated on the horizontal axis. The blood flow at zero (atmospheric) pressure is given an index value of 100 in each case. During the application of local pressure similar decreases in blood flow were demonstrated by both methods.

velocity of venous flow, and out of proportion to the reduction it causes in the minute volume of blood flow. That is, a given particle in the venous blood travels a greater *distance* during a second, although the total *volume* of blood flowing through the vessel during the second is decreased. The explanation offered is that local compression so reduces the cross-sectional area of the veins that there is acceleration of flow even though there is a reduced minute volume of flow through them. This explanation is supported by the finding that acceleration of venous flow during local compression is most marked in persons, particularly old people, with large dilated veins.

A phenomenon of great interest physiologically, but perhaps of little value clinically, was noted during experiments with blood pressure cuffs

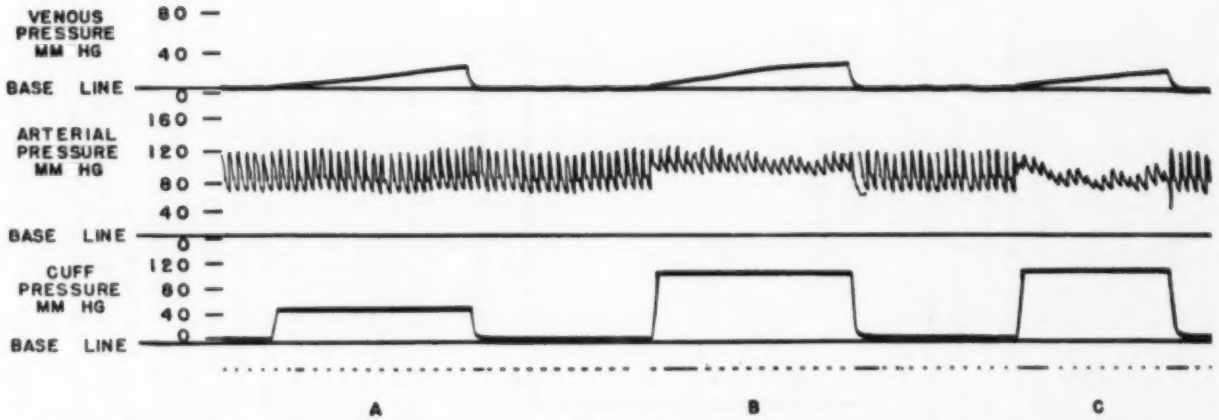


FIG. 10. Optical record of antecubital venous pressure, brachial arterial pressure, and upper arm cuff pressure, all measured with Hamilton manometers in a normal subject. With an upper cuff pressure midway between systemic diastolic and systolic arterial pressures (B), there was an immediate rise in distal "diastolic" pressure, and a more rapid rise in venous pressure than when lower (A) or higher (C) cuff pressures were used.

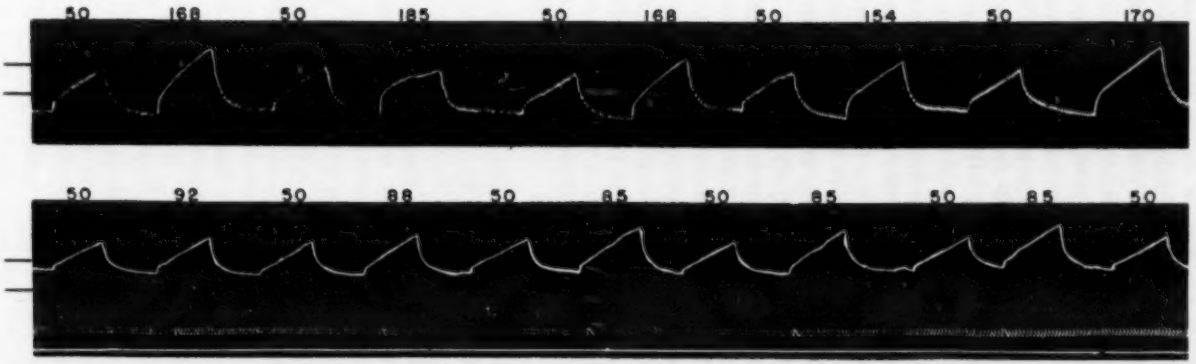


FIG. 11. Plethysmographic tracings of blood flow in the forearm of a subject with arteriosclerotic and luetic disease of the aorta and an arterial pressure of 190/60 mm. Hg (upper tracing) and of a normal subject with an arterial pressure of 100/55 mm. Hg (lower tracing). The collecting pressure applied in the upper cuff for each measurement of blood flow is given in millimeters of mercury just above the respective flow. The scale appended at the left indicates a volume of 5 c.c. The time marks at the bottom are in seconds. The steepness of the blood flow curves indicates the rate of blood flow. Note that alternate control measurements with an infradiastolic collecting pressure (50 mm. Hg) are less steep than measurements with supradiastolic collecting pressures (within limits), and that the pulsations are greater. When too high a collecting pressure was applied (fourth flow, upper tracing), the measurement was less steep than the controls.

applied at greater than diastolic pressure on the limbs.[9] There was an immediate elevation of the diastolic (and a maintenance of systolic) arterial pressure measured with a needle in an artery distal to the cuff (figure 10). This diastolic elevation was instantaneous upon application of the pressure, and disappeared simultaneously with the release of the pressure. It was present only at certain cuff pressures (about mid-way between diastolic and systolic arterial pressure). The diastolic elevation was smaller if too high a cuff pressure was used, whereupon the systolic pressure fell distally; occasionally, the diastolic too was lowered. The mechanism of this effect apparently is that the cuff exerts a valve action on the peripheral arteries and prevents the diastolic fall in pressure normally due to central reflux or "run-off" of pressure. That this rise in distal arterial pressure was real, and effective in increasing blood flow in the distal part, was shown both by the associated more rapid rise in venous pressure (figure 10), which began to increase immediately on inflation of the cuff, and also by direct plethysmographic measurements (figure 11). Naturally, the increase in blood flow persisted only for a brief period, until the venous pressure had risen enough to offset the rise in arterial pressure. The correct cuff pressures, as well as the appropriate times of inflation, could be ascertained for any one limb only by actual intra-arterial pressure and/or plethysmographic tracings. For this reason the method would have little or no practical value. However, it was of interest in demonstrating again the positive effects of changes in local arterial pressure upon local blood flow.

Discussion

Some of the results described in this paper have a practical bearing on the therapy of peripheral vascular disease. For example, reflex sympathetic vasomotor activity may be as important as local vasodilating factors in determining blood flow in the limbs. Furthermore, release of sympathetic vasoconstriction, as from warming the body, can have little adverse effect, except possibly through some side loss of arterial pressure in the proximal parts of distally affected limbs. Indeed, the patchy areas of gangrene that may appear in ischemic feet after a lumbar sympathectomy may be due, at least in part, to this mechanism. On the other hand local vasodilating methods, which in normal limbs produce marked increases of blood flow, may in diseased limbs not only fail to produce significant hyperemia but cause local tissue damage. Thus, the local application of heat, except of the most moderate and rigidly controlled sort, is a dangerous procedure in ischemic limbs which burn very easily. Likewise, attempts to cause local "reactive hyperemia" in limbs already ischemic appear not only futile but also hazardous, since extreme care is necessary in order to avoid traumatizing already devitalized tissues.

During Buerger's exercises a side loss of arterial pressure in the proximal vasodilated muscles may deprive the more distal and more needy parts of blood flow. Furthermore, muscular activity or tension in a limb greatly

increases the utilization of and the need for oxygen. For these reasons it may be desirable in certain patients to use *passive* rather than active intermittent dependency. The definite increases in blood flow and oxygen tension found in the dependent limb would support such therapy. However, there seems to be no sound basis for elevation of the limb above the horizontal; on the contrary, a definite contraindication exists, since this procedure decreases blood flow.

No evidence was obtained in support of the rationale of intermittent venous congestion to relieve ischemia. In fact, all the data were in agreement that this procedure retards the blood flow. Admittedly, however, no observations were made bearing on the subsequent development of collateral circulation, a most important consideration in cases of peripheral vascular disease.

Apparently, local pressure of any degree reduces the blood flow in a part. Therefore, the pressure of dressings, casts, and even of the bedclothes on the limb, or of the limb upon the bed, should be avoided so far as possible. When linear acceleration of venous flow is highly desirable—for example, in order to prevent phlebothrombosis—and when arterial inflow is adequate even with local mild pressurization, the use of elastic stockings or other types of local compression may be clinically useful.

It is hoped that these physiologic observations will be of benefit in the future physical therapy of peripheral ischemic vascular disease. At least they may help to emphasize that every case must be carefully evaluated, physiologic needs clearly defined, and therapeutic methods critically scrutinized before they are applied.

BIBLIOGRAPHY

1. Wilkins, R. W., Doupe, J., and Newman, H. W.: The rate of blood flow in normal fingers, Clin. Sc. **3**: 405–411, 1938.
2. Wilkins, R. W., and Eichna, L. W.: Blood flow to the forearm and calf. I. Vasomotor reactions: Role of the sympathetic nervous system, Bull. Johns Hopkins Hosp. **68**: 425–449, 1941.
3. Eichna, L. W., and Wilkins, R. W.: Blood flow to the forearm and calf. II. Reactive hyperemia: Factors influencing the blood flow during the vasodilatation following ischemia, Bull. Johns Hopkins Hosp. **68**: 450–476, 1941.
4. Doupe, J., Newman, H. W., and Wilkins, R. W.: The effect of peripheral vasomotor activity on systolic arterial pressure in the extremities of man, J. Physiol. **95**: 244–257, 1939.
5. Wilkins, R. W., Halperin, M. H., and Litter, J.: The effect of the dependent position upon blood flow in the limbs, Circulation **2**: 373–379, 1950.
6. Friedland, C. K., Hunt, J. S., and Wilkins, R. W.: Effects of changes in venous pressure upon blood flow in the limbs, Am. Heart J. **25**: 631–647, 1943.
7. Halperin, M. H., Friedland, C. K., and Wilkins, R. W.: The effect of local compression upon blood flow in the extremities of man, Am. Heart J. **35**: 221–237, 1948.
8. Stanton, J. R., Freis, E. D., and Wilkins, R. W.: The acceleration of linear flow in the deep veins of the lower extremity of man by local compression, J. Clin. Investigation **28**: 553–558, 1949.
9. Wilkins, R. W., and Bradley, S. E.: Changes in arterial and venous blood pressure and flow distal to a cuff inflated on the human limb, Am. J. Physiol. **167**: 260–269, 1946.

THE CHANGING NATURE OF PNEUMONIA *

By HOBART A. REIMANN, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

THE cure of many bacterial pneumonias with sulfonamide compounds and with antibiotics has led to an impression that the nature of pneumonia in general has changed greatly in the past decade. The new forms of therapy, especially of pneumococcal pneumonia, shorten the duration of disease, eliminate the causative agent from the sputum, and thereby lessen the incidence and duration of the carrier state. By so doing, it was hoped the spread of infection to others would be retarded and the incidence of pneumonia would decline. While the mortality rate has been reduced, it is by no means so sure that the incidence and the nature of the untreated acute pulmonary infections have changed in proportion. Nor can any form of specific therapy be given all the credit for the present low mortality rate. There has been a steady decline in the death rate of pneumonia in general since 1911, with an exception in 1918–19 caused by pneumonias incident to the pandemic of influenza (figure 1). The rate of decline was greater after 1937, when sulfapyridine was available, and now, with penicillin, has reached the lowest level ever recorded.

Statistics concerning the incidence of pneumonia in general are incomplete, unreliable, and vary as to the kind of pneumonia observed, the location, the kind and age of the patients surveyed, and the care with which diagnoses are made and reported. All acute pulmonary infections, including postoperative, hypostatic and secondary terminal ones, usually are grouped together as pneumonia. The numbers of cases and deaths from all forms of pneumonia reported annually in Philadelphia, for example, between 1930 and 1949, are shown in table 1. The reported incidence, though incomplete, is remarkably uniform from year to year, but the death rate shows a decline after 1938, especially after 1946. The statistics of the mortality rate of lobar pneumonia alone are fairly reliable, but its incidence is a matter of conjecture which was formerly estimated on the basis of the average mortality rate.

PNEUMOCOCCAL PNEUMONIA

Because of the standardization of therapy and its successful results, it is generally supposed that fewer patients with lobar pneumonia now are admitted to hospitals than before 1939. Many patients presumably are successfully treated at home, and those who reach the hospital are sent there because of complicating conditions, or because they do not respond to therapy for other reasons. On the other hand, it is easy to lose sight of the fact that lobar pneumonia was never a common disease. The average practi-

* Presented at the Thirty-First Annual Session of the American College of Physicians, Boston, Mass., April 17, 1950.

From the Jefferson Medical College and Hospital, Philadelphia.

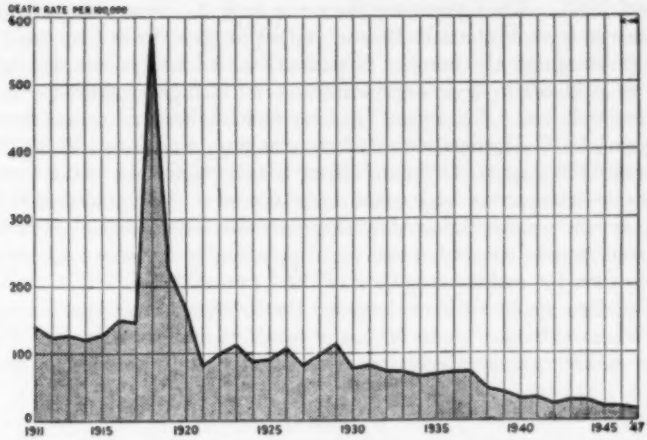


FIG. 1. Behavior of the death rate of pneumonia between 1911 and 1947, Statistical Bull. Metropolitan Life Insurance Co. 29: 9, 1948.

tioner seldom dealt with more than one or two cases a year, but its striking characteristics, its high mortality rate in the past, and its dangerous complications left lasting but exaggerated impressions of its frequency.

Several observers made studies to compare the nature and incidence of pneumococcal lobar pneumonia before and after 1938, when sulfapyridine was introduced. The collected data from such widely separated places as Philadelphia, Cincinnati, Scotland, and New Zealand are in general agreement.

Israel and his coworkers [1] reviewed the statistics at a large city hospital in Philadelphia. In the year 1936–37, 261 cases of lobar pneumonia were admitted, as compared with 312 in 1945–46. Figures from my service,[2] though smaller, are comparable; 75 patients were admitted in the years 1937–40, as compared with 91 in 1946–49. Watson [3] In New Zealand reports 1,139 cases in the years between 1928 and 1937, and 1,087 between

TABLE I

Pneumonia Morbidity and Mortality, City of Philadelphia
Alternate Years 1930 to 1948

	Cases	Deaths		Cases	Deaths
1930	3,552	2,246	1940	3,227	1,120
32	2,791	1,783	42	2,247	1,162
34	3,770	2,131	44	2,217	1,253
36	3,185	2,028	46	2,118	947
38	2,424	1,398	48	2,788	752

(Department of Health, City of Philadelphia, Courtesy of Dr. Angelo Perri.)

1939 and 1948. The figures are shown in table 2. According to information received from Finland in Boston, Tillett in New York City, and Dowling in Washington, the number of patients with lobar pneumonia now admitted to hospitals in their experience has not changed materially from the presulfonamide era. Thompson [4] in Cincinnati, however, reports otherwise. In the years 1936–37, there were 387 cases as compared with 122 in 1948–49. To counter this report, Ordman [5] from South Africa reports a steady increase in the incidence of lobar pneumonia in miners. The increase is limited to natives continually imported to augment the labor forces. The natives come from remote tropical regions and presumably are more susceptible to infection than the stable population of the Transvaal.

From these studies it is evident that the incidence of pneumococcal pneumonia has not changed materially as a result of modern therapy. Fluctuations in incidence have always occurred from year to year in the past and

TABLE II

	Year	Cases	Mortality Per Cent
Israel	1936–37	261	23
	1945–46	312	6.5
Watson	1928–37	1139	19
	1939–48	1087	9.3
Thompson	1936–37	387	37
	1948–49	122	5.7
H. A. R.	1937–40	75	21.3
	1946–49	91	6.6

no doubt will continue to do so. Artificial circumstances, such as the introduction of susceptible persons into endemic areas, as in Ordman's experience, increase the incidence. Natural influences may also play a rôle, as shown by an epidemic of severe pneumonia during an outbreak of influenza A in the Canadian Northwest in 1948.[6] In this outbreak, pneumonias with a high mortality rate reminiscent of those of the pandemic of influenza of 1918–19 occurred in untreated primitive Eskimos. There is no reason to suppose that pneumococci or other bacteria have lost any of their power of invasiveness in recent years.

Pneumococcal Types. Unfortunately, since the determination of types of pneumococci which cause pneumonia is no longer of practical necessity for therapy, the procedure has been almost entirely abandoned. At the Jefferson Hospital, comparison was made of the incidence of specific types of pneumococci causing lobar pneumonia in the three years between 1937 to 1940 and in a comparable period between 1946 and 1949.[2] The results are shown in table 3.

The chief differences, as noted, are a decrease in the number of type 1's from 25 per cent of cases to 12 per cent, and an increase in the higher numbered types from 24 per cent to 49 per cent. Dowling's figures are similar.[7] Thompson reports type 1 as the most common one in 1936–37, and type 2 as most frequent in 1947–48. According to Finland,[8] the distribution of types of pneumococci at present is not much different from previous years. Since the relative incidence and the predominance of types varied from year to year even before 1939, it would seem that no great change has occurred.

Age Group Affected. According to three sets of collected figures, lobar pneumonia now affects an older age group. In one study [1] the greatest number of cases in 1936–37 fell into the 30 to 39 year group; in 1945–46, into the 40 to 59 year group. Watson [3] reports the shift from predominance in the 30 to 59 year group in 1928–37 to the 51 to 79 year olds in 1939–48. In my series in 1937–40, the greater numbers were between 39 and 50, and

TABLE III

Types of Pneumococci

Type	1937–40		1946–49	
	Cases	Per Cent	Cases	Per Cent
I	19	25	11	12
II	7	9	11	12
III	12	16	13	14
V	4	5		
VI	7	9	7	7
VIII	10	13	6	6
Others	16	24	43	49
Total	75		91	

between 41 to 60 in 1946–49. These changes may represent the results of successful prevention or therapy in younger adults and the unchanged or increasing incidence in older persons due to complicating degenerative or other diseases. The advancing age of the population in general cannot be held accountable alone.

Clinical Characteristics. Although no actual figures are available, many observers, including myself, have noted an increase in the number of cases of pneumococcal pneumonia which are clinically "atypical" by not conforming to the characteristics of the "typical" lobar form. In my experience, for example, signs of consolidation were distinct in 84 per cent of patients in the early series, and in only 47 per cent in recent years. In many instances, pneumococci either cannot be isolated from the sputum, or those which are present cannot be classified into the standard types. Previous medication with sulfonamide drugs or penicillin chiefly accounts for the confusion by modifying

the course of the disease and by eliminating pneumococci from the sputum. Only the future can tell to what extent therapy with adrenocorticotropic hormone, cortisone, or other agents will modify the clinical features of pneumonia.

Complications. Surprisingly, modern therapy has not reduced the number of complications to the degree expected. Purulent complications which begin before therapy is started often continue to evolve. According to Israel's figures, complications occurred in 7.3 per cent of patients in 1936–37 and in 4.3 per cent in 1945–46. In Thompson's series the figures are 13 per cent and 11 per cent. In Finland's experience, bacteremia is present in about one-third of patients at present, as it was in earlier years.[8]

Mortality Rate. All observers are in agreement about the decline in the mortality rate of lobar pneumonia. It ranged from 20 to 40 per cent in the pre-antiserum and presulfonamide days and now, as a result of therapy with penicillin, is from 5.7 per cent to 9.3 per cent (table 2). In Anderson's opinion, although the reduction of the mortality rate in the middle age group can be ascribed to modern therapy, the mortality rate in infants continues to be high.[9] The same may be said for the aged. Antipneumococcal therapy, he feels, cannot be improved further, and the mortality rate is now at an irreducible minimum. Any further enhancement of the efficacy of therapy must be directed toward improving the natural resources of the patient himself to overcome infection. Should some unforeseen catastrophe stop the supply or distribution of modern therapeutic agents, the high mortality rate of the presulfonamide era no doubt would be resumed.

The death-rate from pneumonia in patients with chronic alcoholism, pulmonary tumors, bronchiectasis, purulent complications, and other diseases remains high.

Other Pneumonias

Whereas pneumococcal lobar pneumonia, as a rule, is a sporadic endemic disease with a remarkably uniform incidence from year to year, pneumonias caused by hemolytic streptococci, staphylococci, *H. influenzae*, *Kl. pneumoniae* and other bacteria, by psittacosis and by various filtrable viruses occur so infrequently or in such localized outbreaks that few statistics of their incidence are available. These pneumonias do not conform clinically to the classical picture of lobar pneumonia and are regarded as atypical. Pneumonia caused by secondary bacterial infection during epidemics of influenza, and pneumonias caused by presumed viruses, come and go in epidemic waves at unpredictable intervals. When they are temporarily prevalent, the usual pattern of pneumonia as encountered in practice of course changes. An occurrence of this kind of atypical pneumonia is illustrated by the great increase in the mortality rate of pneumonia caused by various pyogenic bacteria incident to the pandemic of influenza in 1918–19 (figure 1), and by the recent localized epidemic in Canada.

Another example took place between 1941 and 1943, when "viral" pneu-

monias became pandemic. The small outbreaks observed in 1938 and 1939 were forerunners of the widespread disease of the next few years.[10] Viral pneumonias at that time represented the severest forms of a mild infection of the respiratory tract, and appeared in the proportion of one pneumonia to every 10 nonpneumonic mild cases. The pneumonias themselves occurred three or four times as often as lobar pneumonia, but the mortality rate was less than 1 per cent.[11]

In the absence of perspective at the time, suggestion was made that viral pneumonias underlay most bacterial pneumonias, and the removal of the bacterial superinfection by modern therapy after 1939 simply unmasked the viral disease and left it to be recognized.[12] However, since the pandemic ended leaving pneumonia at present about the same as before, it is obvious that viral pneumonia is a separate disease and the increase in the number of cases was real. No large outbreaks have been recorded since then but, in keeping with other epidemic diseases, a recurrence may be anticipated.

In addition to epidemic viral pneumonia, just discussed, another form of "viral" pneumonia was described in 1938.[10] It is clinically identical with the epidemic form but is uncommon, sporadic, nonseasonal, severe, rarely fatal, and, like lobar pneumonia, seems to occur with more or less uniform incidence from year to year. It is seldom accompanied by mild, nonpneumonic disease in other patients. Since the cause of neither form is known, there is no way of telling whether the epidemic and sporadic forms are etiologically the same. They are likely to be different and, in themselves, may be composed of separate entities.

As described elsewhere, severe, sporadic "viral" pneumonias often give rise to diagnostic and therapeutic problems.[13] They may be confused with pneumococcal pneumonias, naturally atypical in nature or made so by insufficient therapy, or with acute pulmonary tuberculosis, psittacosis, and typhoid. Severe viral pneumonia may also resemble the newly recognized uncommon diseases, Q fever, ornithosis, coccidioidomycosis, and histoplasmosis, which were not even considered before 1938.

"Viral" pneumonias and several of the diseases just mentioned were discovered almost synchronously with the introduction of the sulfonamide compounds. Interest in them occasionally diverted attention from the well-known lobar form, and made a change in the nature of pneumonias dealt with in practice apparent but not real. The "new" diseases have always been present but in the past were unrecognized, or regarded as unclassifiable bronchopneumonias, or ignored in favor of the more fatal pneumococcal pneumonias.

It is highly desirable that etiologic diagnosis be made in all cases of pneumonia, since different entities need different antibiotic therapy. From an epidemiologic point of view, it is desirable that several key diagnostic centers strategically placed as observation posts throughout the country, continue to determine the cause of all forms of pneumonia as they appear and the type of pneumococci prevalent.

Conclusion

A change in the character of pneumonia in general occurs from time to time and depends chiefly on the presence or absence of certain epidemic forms of pneumonia, especially those caused by, or presumably caused by, viruses. The latter are apt to be widespread, and to come and go in keeping with the natural waves of epidemic behavior. The 1941–43 pandemic of the disease of which "viral" pneumonias were an integral part disturbed the statistical balance of cases at that time. Staphylococcal, streptococcal, Q fever pneumonia and others are uncommon diseases but may occur in small localized outbreaks. In spite of impressions to the contrary, several studies indicate that the incidence of pneumococcal lobar pneumonia is remarkably constant, and was not significantly disturbed after 1939 either by the introduction of sulfonamides and antibiotics or by the transient pandemic of "viral" pneumonias. As in previous years, the character of lobar pneumonia is subject to variation from year to year in accordance with the predominance of pneumococci of different types.

Modern therapy has caused a change in the clinical characteristics of lobar pneumonia. In adequately treated patients, the course of the disease is shortened and the death rate has been reduced. Insufficient therapy may modify the disease so as to confuse diagnosis with various kinds of atypical pneumonia. The recognition of previously unknown forms of pneumonia, such as "viral" pneumonia, Q fever, ornithosis, and others, adds to diagnostic and therapeutic complexity. It is essential to establish etiologic diagnoses in all pneumonias, since different entities respond to different antibiotic agents and demand special epidemiologic management.

BIBLIOGRAPHY

1. Israel, H. L., Mitterling, R. C., and Flippin, H. F.: Pneumonia at the Philadelphia General Hospital, 1936–1946, New England J. Med. **238**: 205–212 (Feb. 12) 1948.
2. deAndino, A. M., and deBeradinis, C. T.: Am. J. M. Sc. To be published.
3. Watson, M. H.: Two decades of lobar pneumonia: a study of the incidence and mortality rate of lobar pneumonia as seen in the Wellington Hospital during the past twenty years, New Zealand M. J. **48**: 371 (Aug.) 1949.
4. Thompson, R. T., and others: Pneumococcus types, mortality, bacteremia and purulent complications in primary pneumococcus pneumonia at the Cincinnati General Hospital, 1936–1949 (Abst.), J. Lab. and Clin. Med. **34**: 1757–1758 (Dec.) 1949.
5. Ordman, D.: The incidence and control of pneumonia in the native labourers of the Witwatersrand Goldfields with special reference to the tropical natives, Proc. Transvaal Mine Officers Assn. **28**: 75–83 (Mar.) 1949.
6. Nagler, F. P., van Rooyen, C. E., and Sturdy, J. H.: An influenza virus epidemic at Victoria Island, N.W.T., Canada, Canad. J. Pub. Health **40**: 457–465 (Nov.) 1949.
7. Dowling, H. F., Rotman-Kavka, G., Hussey, H. H., and Hirsh, H. L.: Treatment of pneumococcic pneumonia with oral and intramuscular penicillin, Am. J. M. Sc. **213**: 413–417, 1947.
8. Personal communication to the author.

9. Anderson, T.: Pneumonia—a survey—past and present, Edinburgh M. J. **55**: 705–720 (Dec.) 1948.
10. Reimann, H. A.: An acute infection of the respiratory tract with atypical pneumonia. A disease entity probably caused by a filtrable virus, J. A. M. A. **111**: 2377–2384 (Dec. 24) 1938.
11. Reimann, H. A.: The viral pneumonias and pneumonias of probable viral origin, Medicine **26**: 167–219 (May) 1947.
12. Francis, T.: Virus pneumonia, Canad. J. Pub. Health **35**: 49–54 (Feb.) 1944.
13. Reimann, H. A.: Severe, sporadic "viral" pneumonias. Diagnostic and therapeutic problems, J. A. M. A. **144**: 81–85 (Sept. 9) 1950.

THE INHERITANCE OF SPONDYLITIS RHIZOMELIQUE (ANKYLOSING SPONDYLITIS) IN THE K. FAMILY *

By Herman H. Riecker, M.D., F.A.C.P., James V. Neel, Ph.D., M.D., and Avery Test, Ph.D., *Ann Arbor, Michigan*

Spondylitis rhizomelique, an ankylosing arthritis of the spine generally associated with the names of von Bechterew, Marie, and Strümpell, is a disease of obscure etiology. In the early work on this condition, Magnus-Levy [1] drew attention to the association of spondylitis rhizomelique and rheumatoid arthritis of the extremities, and the disease is now generally regarded as a form of rheumatoid arthritis, although there are dissenting opinions.[2, 3] Many factors have been implicated as causative agents. The present report records in some detail a kindred in which at least five members have ankylosing spondylitis, and considers the part that an hereditary influence may play in the appearance of the condition in this and other families.

Hereditary factors are of demonstrated importance in the etiology of hypertrophic arthritis,[4, 5] the arthritis of gout [6, 7, 8] and rheumatic fever,[9] and some of the mixed arthritides.[10, 11, 12] Thus far, however, evidence for an hereditary factor in the etiology of rheumatoid arthritis has been scant, although Dawson and Tyson [13] found that in 100 cases of rheumatoid arthritis an immediate member of the family was similarly affected in 15 instances, and Robecchi (quoted from 3) obtained positive family histories in 30 per cent of his patients. In Still's disease, usually regarded as juvenile rheumatoid arthritis, Coss [14] also found that 30 per cent of the family histories were positive for rheumatic fever, arthritis, and arthralgia.

Spondylitis rhizomelique has resembled other types of rheumatoid arthritis in the poor definition of hereditary factors. It is true that von Bechterew's original description of this disease in 1893 [15] pointed to the influence of heredity. In the first of his cases, the mother, a sister, and a child of the patient were said to be similarly affected; in the second, the mother and an aunt; and in the third, the mother. Marie and Astié in 1897 [16] reported the case of a man with marked kyphosis whose sister and father were likewise affected. Magnus-Levy in 1902 [1] reported four cases, one of whom had two maternal uncles with similar symptoms. However, these early reports of the supposed familial occurrence of spondylitis rhizomelique have been accepted with reservations, since the clinical history was in some instances not

* Received for publication September 30, 1948.

From the Staff of St. Joseph's Mercy Hospital, Ann Arbor, Michigan; the Department of Human Heredity, Laboratory of Vertebrate Biology, University of Michigan, Ann Arbor, Michigan.

Grateful acknowledgment is tendered the Board of Governors of the Horace H. Rackham School of Graduate Studies of the University of Michigan for their support of this study.

The references quoted here are only some of the more recent, key references to an extensive literature.

typical of the disease, and they, of course, lacked roentgen confirmation. The validity of some of von Bechterew's cases has in particular been challenged.[20] Furthermore, the diagnosis in relatives of the patients, with only a few exceptions, rests entirely on hearsay evidence, the unreliability of which is nowhere better demonstrated than in family histories of "back trouble."

During the three decades following these early reports, the literature on spondylitis rhizomelique, so far as we have been able to find, with one exception was devoid of references to an hereditary factor in the etiology of the disease. This exception is a paper by Geilinger,[17] who in 1918 reported the most extensive pedigree recorded up to the present time; a patient with an affected brother, maternal uncle, maternal aunt, maternal grandmother, and possibly an additional maternal aunt.

More recently, since 1930, there have appeared a number of references to a familial incidence of the disease. For the most part these references are the outgrowth of casual observation rather than the result of systematic studies on the rôle of heredity in this disease. Weil and Allolio,[18] Ehrlich,[19] Blair,[20] Dekkers,[21] Reynolds (quoted from 21), and Stecher and Hauser [22] have all recorded the occurrence of the disease in brothers. Fischer [23] refers briefly to the occurrence of the disease in two generations, including two siblings in one generation. Herrick and Tyson [24] have also described the disease in two generations, father and son.

In view of the frequency of the condition and the many other reported cases in which there is no positive family history, these reports—assuming that all are valid—are relatively isolated and scarcely constitute significant evidence for the operation of genetic factors.

Claussen and Kober,[25] on the other hand, studied systematically the families of 10 persons with spondylitis rhizomelique, selecting the index cases only on the basis of the availability of their families for study. In four of these 10 families, one additional case of ankylosing spondylitis was discovered, in one family two additional cases, and in one family, three additional cases were found. No simple pattern of inheritance was observed. There was a very noteworthy incidence of "articular rheumatism" (Gelenkrheumatismus) in other members of these families.

The criteria for the diagnosis of spondylitis rhizomelique have been adequately reviewed by many authors (cf. esp. Comroe [26]). In brief, the diagnosis rests on the clinical history of low back pain, with onset usually in the twenties, the finding of a rigid, "poker" spine, an elevated erythrocyte sedimentation rate, and a characteristic roentgen picture of obliteration of the sacroiliac joints and calcification of the paravertebral ligaments. A markedly decreased chest expansion, caused by involvement of the costovertebral joints, is a characteristic finding. The occurrence of rheumatoid arthritis in other joints is valuable additional evidence of the disease in the presence of low back pain. About 90 per cent of the affected persons are males.

Presentation Of Data

The kindred in question came to our attention when a patient (III 22 (cf. figure 1)) consulted the senior author because of pain and stiffness in his back, diagnosed as typical spondylitis rhizomelique on the basis of characteristic roentgen findings and an increased erythrocyte sedimentation rate. Subsequently a sister of this man (III 24) was seen with similar complaints. When a history was obtained of an affected parent, and other affected near relatives, an attempt was made to see as many of the kindred as possible, and to obtain pertinent information on those not actually examined. Data were obtained on 87 persons (including spouses), of whom 40 were seen by the authors. In addition, medical records were available on two others. Nine of the remaining 45 persons are dead.*

A majority of the kindred lives in Ohio and Michigan. As many individuals as possible were examined at St. Joseph's Mercy Hospital, Ann Arbor, and at the Heredity Clinic of the University of Michigan. When it was not feasible to study individuals at those places, they were visited in the home, a circumstance which, together with problems of coöperation, unfortunately made as complete an examination as would be desired impractical in some cases.

Although the classical feature of ankylosing spondylitis, the so-called "poker spine," is unmistakable, there exist all gradations of disability. In this kindred, the members of which are fully aware of a familial tendency to the disease, there is an understandable inclination to attribute every twinge in the back to the "family disease." The classification of any individual who was not actually examined is therefore doubtful, although every effort was made to cross-check our sources of information.

Roentgen examinations of the cervical, dorsal, and lumbar spines were obtained on as many individuals as possible in generation II, and also, when possible, on any other members of the kindred who had symptoms referable to the spine or whose descent made a roentgen-ray of unusual interest. We were fortunate in that several of these individuals had already been studied elsewhere, and reports of the roentgen studies were available. Erythrocyte sedimentation rates were obtained when indicated and possible. In each case so diagnosed, the presence of spondylitis rhizomelique was unequivocal.

Thirty-nine of the individuals who were seen were tested as to the blood groups (A_1, A_2, B, O), the blood types (M, N), the Rh blood types (R^1, r, R^2, R^0, R′, R″, R^z, R^y),† and the ability to secrete the group specific sub-

* The senior author, in addition to locating the kindred, made a number of the medical examinations. Dr. Test was responsible for the initial field work and pedigree. The remainder of the examinations and field work were carried out by Dr. Neel, who also prepared the report. The authors are indebted to Dr. C. W. Cotterman of the Heredity Clinic for assistance in certain phases of the field studies. We are also indebted to Dr. S. W. Donaldson and his staff of the St. Joseph's Mercy Hospital for permission to reproduce the roentgen studies of figures 2 to 5.

† The individuals seen during the early part of the study were only classified as Rh + and Rh −.

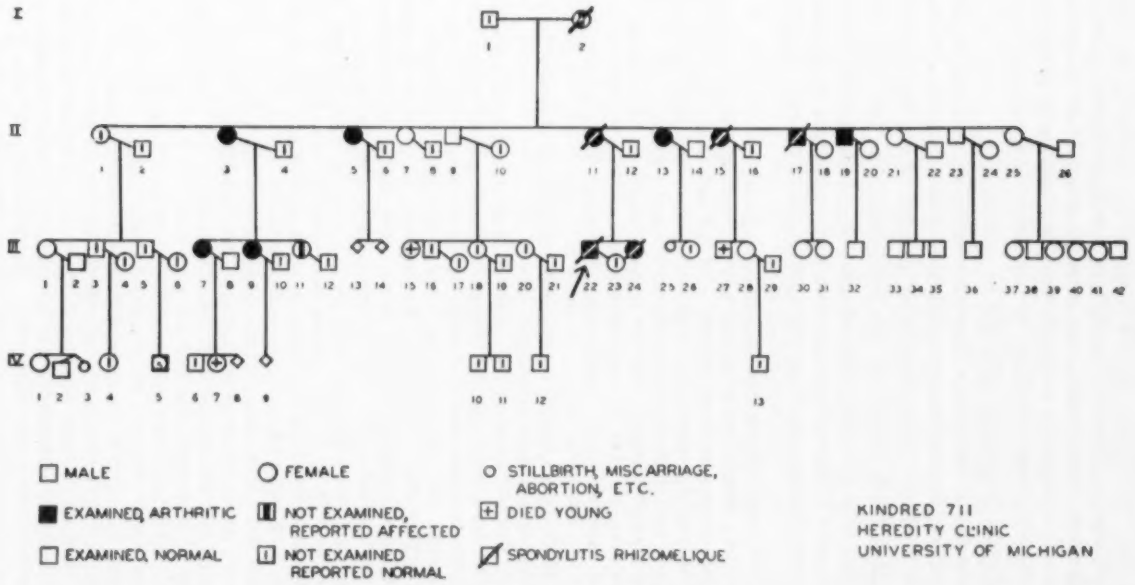


FIG. 1. Pedigree of the K. kindred.

stances in the saliva. Color vision and the ability to taste phenylthiocarbamide were also tested where the individuals were of suitable age, and a hair sample was obtained. These traits all have a well-established genetic basis. The determinations were made in an attempt to establish the presence or absence of genetic linkages, as well as to provide a routine check on paternity. Inasmuch as no evidences of linkage or impaternity were encountered, these negative and space-consuming data will be omitted.

A pedigree of the kindred is shown in figure 1. As will be described below, in addition to ankylosing spondylitis other types of arthritis were present in the kindred. Individuals with arthritis of any type are indicated by appropriate symbols, except the two individuals with traumatic or tuberculous arthritis, who are designated unaffected. A brief description of the pedigree follows. Unless otherwise indicated, spouses will be mentioned only to the extent necessary to rule out inheritance of the trait from them.

I 1. J. H. K., male, died at the age of 69 of apoplexy.

I. 2. F. H. K., female, died at the age of 74, of the sequelae of a fractured hip. She is not known to have had any difficulty with her back until about age 37 when, following the birth of her tenth child, she developed an umbilical hernia and also pain in her back, with progressive loss of mobility and kyphosis. She is regarded as probably having had spondylitis, but the evidence is not clear cut, the age of onset being somewhat atypical. This woman's mother and one of her five siblings, a female, are reported to have developed a similar marked kyphosis when they reached early middle age.

II 1. C. K. C., female, died at the age of 30 following an operation for a "tumor of the bowel" during her fourth pregnancy.

II 2. A. L. C., male, spouse of II 1. Died at about the age of 60, cause unknown.

II 3. B. K. L., female, age 59. About 15 years ago she became subject to episodes of dull lower lumbar and interscapular backache, precipitated by overexertion or "sitting in a draft" and relieved by dry heat and salicylates. During the last four years she has had considerable aching in her fingers and has noted progressive enlargement of the distal phalangeal joints of the right hand. She also has frequent dull aching in her feet and knees. System review was essentially negative except for a long-standing fatty food intolerance, with periodic episodes of right upper quadrant discomfort accompanied by vertigo, nausea and vomiting, and mild diarrhea. An oral cholecystogram 10 years ago is said to have shown "chronic inflammation" and some deformity of the gall bladder, but no cholelithiasis. On physical examination there was observed a robust woman whose spinal mobility and contours were within normal limits for a person of her age and habitus. There were definite Heberden's nodes of the right third and fifth fingers, with radial deviation of the terminal phalanx of the fifth finger. Chest expansion was 4.5 cm. Films of the right hand showed marginal lipping and bone condensation at the distal interphalangeal joints of the middle and little fingers. Films of the dorsal and lumbar spines showed tiny osteophytes and beginning lipping of the sixth to ninth dorsal vertebrae, and early lipping of the anterior margins of the fourth and fifth lumbar vertebrae (Dr. V. A. LaFleur).

II 4. C. H., male, deceased spouse of II 3. As a child he had recurrent attacks of severe "inflammatory rheumatism," but he appeared to make a complete recovery and was active in athletics as a young man. He died at age 31, after a protracted two-year illness during which he saw many different physicians, without any general agreement as to the diagnosis. The illness was characterized by low-grade fever,

progressive anemia, increasing cardiac pain, and—his widow believes—soreness of his fingers. He was told by several physicians that he had a "leakage of the heart." No autopsy was performed. In retrospect it seems possible that, following childhood rheumatic fever, he had residual cardiac damage, with subacute bacterial endocarditis developing at age 29. He is described in some detail because of the histories, to be discussed below, of the three daughters born to him and II 3.

II 5. H. K. N., female, age 58. She had no symptoms referable to her back until three years ago, when she had an abscessed third molar extracted and one day later experienced the onset of severe back pain, confining her to her bed. Roentgen-rays taken at this time showed, according to her physician-husband, some loss of intervertebral disc space and "slight decalcification of the bone." After a month of intermittent bed rest, diathermy, and massage, she was much improved. Two years ago she was shaken up in an automobile accident and the following day had a return of her back pain, this time much more severe and persistent. She began to develop kyphosis. Repeat roentgen-rays showed no significant change in her spine except the kyphosis. About a year ago she was studied at the Cleveland Clinic. Nothing significant was found on skull films, sternal marrow biopsy, or numerous blood studies. She received a course of penicillin injections, together with intensive diathermy treatments. A back brace was fitted, and there has been marked subjective improvement the past year. She volunteered the information that within the past several months she had wondered at times whether her "temples" were becoming more prominent.

About two years ago the patient began to notice occasional purpuric areas of the corneae and during the past year she has, in addition, been subject to spontaneous ecchymotic areas over her body, and has noted a tendency to bruise easily.

Her past history is significant in that about age 17 or 18 she had acute rheumatism of her left upper extremity of a week's duration, during which her elbow and hand were swollen, hot, and tender. At about age 27 she developed exertional dyspnea and became aware of a "noise" in her chest. She was found to have a "musical murmur," which gradually disappeared. However, one year ago she had influenza and following this again developed dyspnea, and a murmur was again heard.

She was seen briefly. There was a mild scoliosis but no joint deformity. Head appeared normally proportioned. There were ecchymotic areas on the right arm and forearm. Chest expansion was 4 cm. Further examination was not performed. This patient presents a complex picture. It seems quite possible that she had rheumatic fever as a young woman, with some residual cardiac damage, as shown by the "musical murmur." Her present arthritis fits into no simple pattern, although several possibilities suggest themselves.

II 6. G. E. N., male, 65. Normal spouse of II 5.

II 7. M. K. B., female, age 56. At age 16 she fell and "dislocated" her right hip. She recovered from the injury very slowly, and a year later a diagnosis of tuberculosis of this same hip was made and two operations were performed. Her right leg has been shorter than the left since this time, with fusion at the hip joint. In the past several years she has had frequent acute, incapacitating attacks of vertigo, accompanied by nausea and vomiting, for which she has been studied by several physicians. These studies have included essentially negative oral cholecystograms and gastrointestinal series. During these studies she inquired about her back and was told that it showed the changes normally present at her age. At the Cleveland Clinic, where she was studied most thoroughly, the attacks were thought to be due to a labyrinthine disturbance. When seen in the home she showed no significant loss of mobility of the spine, or deformity, aside from that relating to the right hip.

II 8. E. B., male, spouse of II 7. Died at the age of 59 of a cardiac affection.

II 9. W. H. K., male, age 55. We have not seen this man, but he was examined at the University of Michigan Hospital at age 52 because of anginal pain. At that

time he had no complaints suggestive of arthritis, and no observations consistent with this disease were recorded.

II 10. J. S. K., female, age 52. Spouse of II 9. In reply to a questionnaire she stated she had arthritic pains in her knees and hands.

II 11. F. K. F., female, age 53. She first began to have severe backaches at age 24, during her second pregnancy. These persisted after delivery and became worse four years later, following an attack of influenza. Loss of spinal mobility and kyphosis developed gradually. Roentgen-rays of her lower spine and sacroiliac joints at the age of 43 revealed a severe arthritis characterized by synostosis of both sacroiliac joints, calcification of the paraspinous ligaments with ankylosis of the vertebrae, and a decrease in the intervertebral spaces (Dr. F. J. Eakins). Many different therapeutic measures were assayed, but most relief of pain was obtained following a course of deep roentgen-ray therapy at age 50. The vertebral column is now ankylosed in a position of moderate kyphosis, and she no longer has back pain.

II 12. C. F., male, age 56. Divorced spouse of II 11, reported normal.

II 13. A. K. H., female, age 51. At the age of 43 she experienced a sudden onset of generalized joint pain and stiffness of such severity that only with great difficulty could she turn over in bed. Symptoms increased for several months and then gradually disappeared. During the three months of severe pain, the distal phalangeal joints became more prominent, with subsequent regression. As nearly as she can recall, menopausal symptoms appeared shortly before or at about the time of the arthralgia. Menopause was at age 45. Like several other members of this sibship, she has a fatty food intolerance, with periodic right upper quadrant pain accompanied by nausea and vomiting. When seen in her home, the only noteworthy feature observed was slight enlargement of the distal phalangeal joints, which was not considered significant.

II 14. W. H., male, age 53. Spouse of II 13. Has had pain in his left elbow and shoulder the past year, and roentgen-ray studies were interpreted as "arthritis of the elbow."

II 15. H. K. R., female, age 49. She first noted pain and stiffness of the back at age 18, with marked increase in her symptoms at age 21, during and following her first pregnancy. She gradually developed kyphosis, and also began to experience difficulty in walking, due to loss of mobility of the hip joints. This progressed to complete immobilization of the hip joints. There was back pain during all this time. Past history included a hysterectomy at age 28 because of uterine fibromata.

Examination revealed an obese woman whose spine was fixed in moderate kyphosis. There was no detectable motion at the hip joints. Chest expansion was limited to 1 cm.; breathing was abdominal in type. Spleen was palpable, whether due to splenomegaly or because of lowered diaphragms was not clear. Sedimentation rate was 23 mm./hour. Roentgen-rays were limited to the pelvis and hips, and showed complete loss of disc space at the fourth-fifth lumbar joint and the lumbosacral articulation, with calcification of the paraspinous ligaments. There was obliteration of the sacral articulations, and almost complete obliteration of both hip joints (Dr. S. M. Donaldson) (figure 2). A course of 12 deep roentgen-ray treatments was carried out, with marked subjective improvement. Vitallium cup arthroplasty for the hip joints was recommended.

II 16. R. W. R., male, age 46. Normal spouse of II 15.

II 17. W. H. K., male, age 46. At age 18, following a fall, he developed back pain, at first confined to his lower back. During the past 25 years the site of his discomfort has gradually shifted upwards, so that now the maximum pain is in the cervical region. There has been progressive kyphosis. Examination revealed an undernourished male whose chest expansion was 1 cm. The spine was fixed in moderate flexion. There was marked limitation of movement at the hip joints. Sedi-

mentation rate was 24 mm./hour. Antero-posterior and lateral films of the spine revealed loss of disc spaces and calcification of the paraspinal ligaments the entire length of the spine, with apparently complete fixation of every vertebral body. There was obliteration of the sacroiliac articulations, and loss of the joint space in both hips (Dr. S. M. Donaldson) (figures 3a and 3b). The patient was given a course of eight deep roentgen-ray treatments to the dorsal and cervical spine, with subjective improvement.

II 18. M. O. K., female, age 36. Normal spouse of II 17.

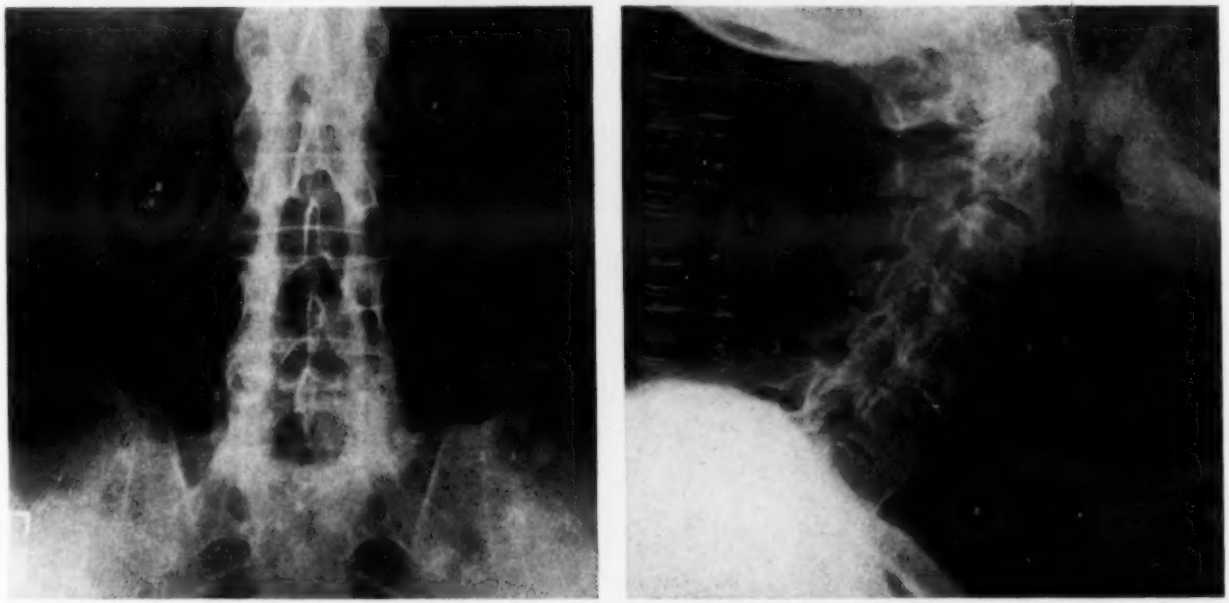
II 19. R. K., male, age 45. Ten years ago he first experienced intermittent pain in the lumbar region, radiating into the posterior aspect of his lower extremities. Treatment by various physicians has been directed towards eradicating focal infection,

FIG. 2. H. K. R., female, age 49. Fusion of the hip and sacroiliac joints. Calcification of the paraspinous ligaments of the last lumbar vertebrae is also evident.

by prostatic massage, tonsillectomy, extraction of teeth, and hemorrhoidectomy. He had been practically asymptomatic for several years until three months before we saw him, when he experienced an exacerbation of his previous symptoms. Physical and neurological examination was essentially negative. There was no detectable limitation of motion in the spine. Chest expansion was 4 cm. Sedimentation rate was 22 mm./hour. Complete roentgen-rays of the spine were interpreted as within normal limits except for slightly increased density of the right sacroiliac region as compared with the left; this was not thought to be significant. A definite diagnosis was not reached in this case, but early spondylitis appeared to be a real possibility.

II 20. P. L. K., female, age 36. Normal spouse of II 19.

II 21. L. K. M., female, age 43. History and physical examination essentially negative.



a b

FIG. 3. W. H. K., male, age 46. a. Extensive calcification of the paraspinous ligaments in the lumbar region, resulting in the classical "bamboo spine" of spondylitis rhizomelique. There is also almost complete obliteration of the sacroiliac articulations. b. Cervical spine of same patient, illustrating the involvement of the paraspinous ligaments in this region.

II 22. C. C. M., male, age 61. Spouse of II 21. He has a long medical history without, however, any suggestion of arthritis.

II 23. J. M. K., male, age 40. He injured his right wrist while boxing at age 20, with subsequent stiffness and occasional pain in the wrist. Roentgen-rays taken several years ago and made available to us showed an aseptic necrosis of the right lunate bone. He has no symptoms referable to his back, and physical examination as well as full length roentgen-rays of his back were negative. Chest expansion was 12 cm.

II 24. C. P. K., female, age 36. Spouse of II 23. She has had occasional discomfort in her lower back ever since she "strained it" lifting a heavy object at age 29. For the past five years she has had occasional pain and stiffness in the right hand and some swelling, with shooting pain in the right third finger. The left hand is affected to a lesser degree. Complete physical examination as well as films of the lumbosacral area and hands were negative for objective signs of arthritis.

II 25. E. K. U., female, age 36. A hysterectomy was performed several years ago because of a "fibroid tumor." History was otherwise unremarkable, as was physical examination.

II 26. L. J. U., Sr., male, age 36. Normal spouse of II 25.

III 1. L. C. R., female, age 41. She was involved in a serious automobile accident at age 19, with "sacroiliac strain and dislocation of two vertebrae." Roentgen-rays taken seven years later, at the time of her first pregnancy, were said to have shown partial fusion of some of the lumbar vertebrae; this was attributed at the time to the accident. This person's mother, II 1, died at age 30, without having shown any signs of spondylitis or any other form of arthritis. However, the possibility had to be considered that II 1 would have developed the disease later, that she had transmitted the susceptibility to her daughter, and that the change attributed to accident was really a mild spondylitis. L. C. R.'s past history included a cholecystectomy in 1928 and a hysterectomy in 1941 because of a "fibroid tumor." Physical examination revealed an obese woman with slight loss of lumbar flexion. Complete roentgen-ray studies of the spine were negative; there was no evidence of old injury.

III 2. E. B., male, age 56. Normal spouse of III 1.

III 3. L. C., male, age 39. Reported normal.

III 4. M. C., normal spouse of III 3.

III 5. D. C., male, age 37. Reported normal.

III 6. F. C., normal spouse of III 5.

III 7. T. H. S., female, age 39. This individual is the eldest of the three daughters of II 3 and 4 (q.v.). At age 8 she had an episode of severe acute nephritis, followed by persistent albuminuria. Hypertension was discovered at age 19, during her first pregnancy, when she developed pre-eclampsia. A second pregnancy, at age 25, also resulted in pre-eclampsia, and labor was induced at seven and one-half months. There have been several episodes suggestive of mild hypertensive crises in the past year. She has been subject to severe lumbar backaches since girlhood. For the past two years she has had episodes of back pain centering somewhat higher, in the lower thoracic region, and radiating anteriorly in girdle fashion. The pain, when present, is exaggerated by deep breathing. The backaches are often precipitated by exposure to inclement weather or an activation of a chronic sinusitis. The blood pressure taken in her home was 168/128 mm. Hg. There were no joint deformities. Flexion of the spine appeared to be limited in that she could not bring her chin closer than 3.5 cm. from her chest, and lacked 10 cm. of reaching the floor on straight-legged bending over. Chest expansion was 2.5 cm. Eye grounds showed grade I hypertensive changes. Heart sounds were normal. There was a slight pretibial edema. Antero-posterior and lateral films of the dorsal and lumbar spines revealed slight marginal lipping and bone condensation along the anterior margin of the third through the

seventh dorsal vertebrae, with slight narrowing of the intervertebral spaces between the fifth and sixth and the sixth and seventh dorsal vertebrae (Dr. V. A. LaFleur).

III 8. H. S., male, age 38. Normal spouse of III 7.

III 9. D. H. F., female, age 36. At age 8 or 9 this patient experienced severe "growing pains," by which she apparently means generalized aching in both muscles and joints. These pains have persisted in some degree up to the present time, with exacerbations precipitated by overwork, psychic upsets, and changes in barometric pressure. The fingers, wrist, elbows, toes, heels (knees, back, and temporomandibular joints have all been affected at one time or another. During an attack there is said to be cutaneous hyperesthesia over the affected area, with slight swelling and local heat of the joints involved. General health has been poor. Operations include appendectomy, tonsillectomy, and subtotal hysterectomy because of "fibroids." There is a history of chronic sinusitis and gall bladder disease. Finally, four years ago, there was an episode characterized by dependent edema, which disappeared after a month of bed rest. The heart was said to be enlarged at the time. Superficial appraisal of this woman in the home revealed nothing of significance; chest and abdomen were not examined. Antero-posterior and lateral films of the dorsal and lumbar vertebrae revealed very minimal changes of the degenerative type in the mid-dorsal region, similar to those seen in her sister, III 7.

III 10. J. F., male, age 38. Normal spouse of III 9.

III 11. E. H. C., female, age 32. Reported by her sisters, III 7 and 9, to have had severe lumbar backaches for some years, and to have developed on occasion during the past three years stiff and painfully swollen fingers.

III 12. V. C., spouse of III 11, reported normal.

III 13. Ectopic pregnancy.

III 14. Ectopic pregnancy.

III 15. T. K., female, died age 3 of "inflammation of the bowel."

III 16. A. K., male, age 29. Reported normal.

III 17. Deceased spouse of III 16.

III 18. J. K. C., female, age 26. In answer to a questionnaire she stated that her only arthritic symptoms consisted of discomfort and stiffness in her back during and following each of her two pregnancies, but that there had been no symptoms in the two and one-half years since her last child was born.

III 19. W. C., male, age 31. Spouse of III 18, reported normal.

III 20. D. K. P., female, age 23. In answer to a questionnaire she replied that she had had arthritis of her left shoulder and both knees following the birth of her only child two years ago, but that she was at present asymptomatic.

III 21. E. P., male, age 30. Spouse of III 20, reported normal.

III 22. R. F., male, age 34. He is the index case for the kindred. When first seen at age 28 he complained of stiffness and soreness of the back and chest of three years' duration. This was sometimes more of a feeling of pressure than of pain. Physical examination revealed muscle spasm in the lumbar area. There was considerable limitation of lateral motion in the spine, and flexion was largely limited to the hip region, the spine being held relatively rigid. Chest expansion was 2.5 cm. The sedimentation rate was 20 mm./hour. Roentgen studies of the spine revealed uniform decalcification, slight loss of intervertebral joint space, and an increase in the density of the upper and lower borders of the dorsal spine. There was loss of the normal lumbar lordosis. In the antero-posterior view there was a suggestion of lime salt deposits in the spinal ligaments (Dr. S. W. Donaldson). The patient received a course of 12 deep roentgen-ray treatments shortly after his first visit, with marked subjective improvement.

Four months after his first visit on the completion of deep roentgen-ray therapy, the sedimentation rate was 17 mm.; eight months later, 18 mm., and 26 months after

the first visit, the sedimentation rate was 7 mm./hour. Roentgen-rays at this time were similar to the initial films, except for definite partial obliteration of both sacroiliac joints, with increased density in this area, and definite although minimal calcification of the paravertebral ligaments at the level of the fourth and fifth lumbar bodies (Dr. S. W. Donaldson) (figure 4).

The patient was last seen at age 34, after an interval of four years. There had been a partial return of symptoms. Physical examination was essentially as initially recorded. Chest expansion was now 1.5 cm., and respiration was abdominal in type. Sedimentation rate was 28 mm./hour. Roentgen-rays of the spine revealed definite progression of the spondylitis, consisting especially of further obliteration of the sacroiliac joint space and further calcification of the paraspinous ligaments.

FIG. 4. R. F., male, age 34. This film, at age 28, reveals chiefly early stages in the obliteration of the sacroiliac joints. Roentgen-ray therapy gave partial relief for about three years, but symptoms then returned much as before. Four years later the obliteration of the sacroiliac joints had progressed and, in addition, there was definite calcification of the paraspinous ligaments of the lower dorsal and upper lumbar regions.

III 23. H. S. F., female, age 32, normal spouse of III 22.

III 24. E. F., female, age 31. At about age 20 to 21 she began to have pain in her lower back. This increased despite considerable chiropractic manipulation, and in addition she developed pain and stiffness in her neck, and also experienced intermittent weakness in her lower extremities which made it difficult for her to walk. She consulted the senior author at age 27 after her brother (III 22) had received marked symptomatic benefit from deep roentgen-ray therapy. Physical examination revealed a well developed woman with very significant limitation of motion in all directions

in the lumbosacral region. There was a soft blowing apical systolic murmur. The roentgen-ray studies showed early obliteration of the sacroiliac joint spaces but no other definite changes. Sedimentation rate was 25 mm./hour. The symptoms were relieved by deep roentgen-ray therapy and subsequently she joined the WAVES, performing her duties without difficulty. When seen on a follow-up three and one-half years after her treatment, she was asymptomatic except for an occasional "catch" in her cervical and lumbar regions. Physical examination was essentially as noted previously. Roentgen-rays of the spine revealed slight further obliteration of the

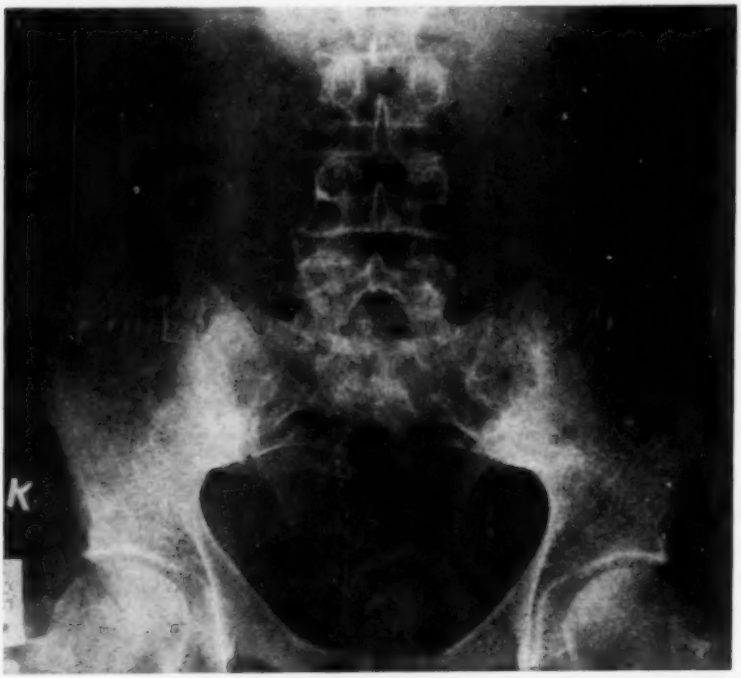


FIG. 5. E. F., female, age 27. This film is interpreted as showing only early obliteration of the sacroiliac joints. The patient was dramatically relieved of her back pain by roentgen-ray therapy. Although she remained asymptomatic, repeat films four years later revealed a slight progression of the obliteration of the sacroiliacs and calcification of the paraspinous ligaments at the level of D12–L1.

sacroiliac joint spaces and definite calcification in the paraspinous ligaments at the level of D12-L1 on the left.

III 25. A child who died age three days. Said to have had congenital heart disease by the attending physician.

III 26. E. H., female, age 23, reported normal.

III 27. R. R., Jr., male, died age five years of a streptococcic septicemia secondary to a barbed wire laceration.

III 28. E. R. K., female, age 28. Her mother, as indicated in figure 1, had

severe spondylitis. E. R. K. was first seen at age 26, when history and physical examination were essentially negative with respect to arthritis. Sedimentation rate was 9 mm./hour. Films of the complete spine were negative. She was seen again at age 28, at which time she complained of intermittent numbness and weakness of her upper and lower extremities of about one year's duration with dull pain of the cervical and interscapular regions of about six months' duration. She had also had some puffiness of her hands. Physical examination was again essentially negative. Sedimentation rate was 12 mm./hour. Complete roentgen-ray studies of the spine were negative. In the absence of any objective findings, diagnosis was deferred.

III 29. R. K., male, age 28. Spouse of III 28, reported normal.

III 30 and 31. R. M. K. and A. K., 9 and 8 year old daughters of II 17, both in good health.

III 32. J. K., male, age 17. The only abnormal finding in this boy was an articulation of the right transverse process of the last lumbar vertebra with the upper border of the sacrum.

III 33, 34, and 35. K. M., G. M., and V. M., 10, 7, and 1 year old sons of II 21. All in good health.

III 36. J. M. K., Jr., male, age 1. Normal infant.

III 37, 38, 39, 40, 41 and 42, the six children of II 25, consisting of P. H. U., female, age 17; L. J. U., male, age 16; E. L. U., female, age 14; J. M. U., female, age 13; C. J. U., female, age 11; and C. A. U., male, age 6. No arthritis was present. However, the four girls all have had a convergent strabismus. P. H. U. underwent corrective surgery at age 6, and E. L. U. at age 4. The other two girls have responded satisfactorily to optical correction.

The fourth generation is composed of 13 children, the eldest of whom is 19. All are reported to be in good health except the eldest, IV 4. He is said to have complained of frequent pains in his back and knees since age 8, and to have episodes of bloody diarrhea attributed, after roentgen-ray studies, to ulcerative colitis, although apparently there has been a difference of opinion concerning the diagnosis. Only two of this generation were seen. IV 1, S. B., was a 14 year old girl in good health. Her brother, IV 2, E. B., age 7, who was a premature twin, showed some residua of a birth injury to the right cortical motor area but no other abnormal findings.

In brief, then, here is a pedigree in which a female who probably developed spondylitis rhizomelique in her late thirties, and whose mother and a sister were probably likewise affected, gave birth to 13 children. One of these is now dead. All of the remaining 12, ranging in age from 36 to 59, have either been seen or are known to us through adequate medical records. Three of the 12 (II 11, II 15, and II 17) have definite spondylitis rhizomelique. The diagnosis rests on a history of chronic backache with onset in the late teens or twenties, a progressive kyphosis with fixation of the spine, roentgen-ray evidence of osteitis of the sacroiliac and apophyseal joints, calcification of the paravertebral ligaments, and an elevated sedimentation rate. Of the remaining nine children, one woman (II 3) has the symptomatology and the Heberden's nodes characteristic of mild to moderate hypertrophic arthritis. One woman (II 13) developed generalized arthralgia for a six month period during her menopause, considered as "menopausal arthralgia." Two persons (II 5 and II 19) have been subject to severe backaches. The first of these (II 5) may have had rheumatic fever as a child, and within the past several years has had episodes of back pain of a rather unusual nature

described above. The second (II 19) has negative spine films and his backache is not amenable to diagnosis by roentgenography. One man (II 23) developed an aseptic necrosis of the lunate bone following an injury sustained during college boxing. Another individual (II 7) "dislocated" her right hip in a fall as a young woman, and a year later is said to have developed tuberculous arthritis of the same joint. Only three persons have been free of joint disease. From the standpoint of the development of arthritic symptoms, some of these individuals are still relatively young and may yet develop initial or additional symptoms.

The third generation ranges in age from one to 41 years. Most of its members are below the age of onset of spondylitis rhizomelique. Of the five children in this generation resulting from marriages between persons with spondylitis and normal individuals, two have spondylitis (including the propositus) and three (ages 8, 9 and 28) are still normal. One marriage in generation II, between a man who probably had rheumatic fever as a boy and a woman who now shows signs of hypertrophic arthritis, yielded three children, all subject to severe backaches and other arthritic symptoms.

In surveying the family as a whole, one gains the impression that not only are the various types of arthritis more frequent than can be explained on the basis of chance alone, but that certain other medical conditions—for which the data are entirely unselected—also have a noteworthy incidence. Of the 13 women in the direct line of descent who have reached an age of 30 or over four have had hysterectomies because of myofibromata. Four of these same 13 have a history suggestive of gall bladder disease, and a fifth has a history that may be due in part to gall bladder dysfunction. Of the six children of II 25 and 26, four have developed strabismus, and two of the four have required surgical correction.

Discussion

In an analysis of the genetic problems raised by this kindred, we may start with the fact that in two generations there occur five proved cases of spondylitis rhizomelique, with the strong possibility that the trait extends back an additional two generations. Unlike most of the other pedigrees cited in the introduction, this is a greater concentration in one kindred than can reasonably be attributed to chance. That this spondylitis is primarily the result of genetic rather than environmental determinants is suggested by the diverse circumstances under which it has first manifested itself, as well as by the failure to elucidate any significant precipitating factor. Generation I of the kindred is known to us only through heresay. Accepting it as a fact that I 2 had spondylitis rhizomelique, then three of her 13 children developed a similar condition, and of the five children of the affected three, two are likewise affected while two are still below the usual age of onset. No person without spondylitis has produced a child with the disease. Two of the definitely affected persons are males and three females. In this

kindred, the condition therefore is transmitted as if due to an autosomal dominant factor or factors whose exact frequency of expression cannot be defined at present.

A comparable situation has been reported for one other form of arthritis, Legg-Calvé-Perthes disease. As in ankylosing spondylitis, the majority of the reported cases are isolated occurrences; occasionally two or more cases occur in the same family. However, Stephens and Kerby [27] have reported one extensive pedigree where the condition is clearly inherited as if due to a single dominant factor. The analogy to our findings may be extended further: although 75 to 90 per cent of persons with Legg-Calvé-Perthes disease are males,[28, 29] in Stephens and Kerby's pedigree there was, as in our pedigree, an approximate equality of affected males and females (16 males: 12 females).

We may next consider the significance of the other types of arthritis present in this kindred. Do they bear some etiologic relationship to the ankylosing spondylitis, in that both depend at least in part on a common causation, or is this association a matter of chance? The significance of the traumatic arthritis of II 23 and the tuberculous arthritis of II 7 is problematical—do these reflect a *locus minoris resistentiae*? There remain four other cases of "arthritis," each differing in important clinical respects from the others (II 3, 5, 13, 19). Such a concentration of joint disease inevitably raises the possibility of an "arthritic diathesis," characterized by an unusual susceptibility of the articular surfaces to various influences in the external and internal environment, the exact nature of which is not yet clear. This concept, of general organ system susceptibilities, has arisen repeatedly (cf. Bauer [30] and Draper, Allen, and Spock [31]). In the literature concerning arthritis, Geilinger,[17] Proebster,[32] Fischer,[23] Miller,[33] and Claussen and Kober,[25] substantiating an impression appearing in the early work on spondylitis rhizomelique,[1] have drawn attention to the association of the disease with rheumatoid arthritis of the extremities and a history of rheumatic fever. The possibility of a relationship between rheumatic fever and rheumatoid arthritis has been mentioned frequently, and the evidence summarized by Dawson and Tyson,[13] Kinsella,[34] and Holsti and Huuskonen,[11] among others. The relationship between rheumatoid arthritis and hypertrophic arthritis is somewhat more debatable; an extreme position has been taken by Pottenger,[35] who writes: "It appears that fundamentally they are the same disease." Finally, Hangarter,[12] after studying an extensive pedigree of mixed, chronic arthritis, wrote of "eine gemeinsame erbliche Minderwertigkeit des Stützgewebes (Bindeknochengewebe)."

Whether there is an "arthritic diathesis," and how far the boundaries of such a diathesis should be extended, must remain moot points for some time, pending further study. But while this is a relationship to be borne in mind, it must also be remembered that arthritis is so common a disease that on the basis of chance alone one can sometimes expect to observe in a

single large sibship multiple occurrences representing several different types. For example, five of the 23 spouses on whom information is adequate or semi-adequate reported arthritic symptoms of some type; these may be regarded as a control group. Many of these spouses are still relatively young; by the time their mean age equals that of generation II, the incidence of arthritis will undoubtedly be higher.

The fact that certain groups of individuals related by common descent appear to have unusual susceptibilities to various groups of medical conditions seems established beyond reasonable doubt. A direct genetic approach to this problem is of course impossible in man, but analogy with the results of experimental genetics provides a completely reasonably explanation. Certain of the known hereditary factors or genes will manifest themselves in every individual who possesses them. These would include the factors responsible for major brachydactyly, certain types of cataract, opalescent dentine, and many others. Other genes are apparently expressed in only a small proportion of those who possess such genes. These include the genes responsible for club foot, harelip and cleft palate, and others. In experimental work with various animal forms, it is possible, starting with a strain in which only a small proportion of individuals exhibit a trait, to produce through selection stocks in which a high proportion show the trait in question. Thus, in the house mouse, typical examples of this include harelip and cleft palate,[36] a type of cataract,[37] open eyelids at birth,[38] and posterior reduplication.[39] This is the result of the accumulation of genetic modifiers in these strains. However, the reverse of this situation may also arise. Quite by chance, certain strains may accumulate a relatively large number of modifiers favorable to the expression of a certain hereditary factor. When that factor is introduced into the strain, it finds conditions unusually favorable to its expression, and there may result a family with an hereditary diathesis. This diathesis may be sufficiently nonspecific to favor the expression of a number of different genes having effects on the same organ system.

The dangers involved in drawing sweeping conclusions from the study of a single pedigree require no comment. Further thorough investigation of *large* kindreds is desirable. In this connection it should be apparent that, from the genetic standpoint, one large sibship of 12 is several times more valuable than four sibships of three each.

As has been pointed out, the ankylosing spondylitis studied in this kindred is typical of that described in the literature. But the pedigree is so unusual that it is not clear whether we are concerned with the action of a genetic factor which is responsible for only a small fraction of the spondylitis rhizomelique, or whether all spondylitis rhizomelique depends on the same "principal determinant," which in this family found itself in an unusually favorable background for its expression.

The ratio of affected males to females is noteworthy. In standard works on arthritis, such as that of Comroe,[26] the ratio of affected males to females

in spondylitis is placed at about 9:1 (see also Polley and Slocumb [40]). The observed ratio of two males to three females is therefore unusual, and becomes even more unusual if the three possibly affected females about whom we have less definite information are included. Geilinger's three-generation pedigree [17] showed the same departure from the usual sex ratio, as did some of the earlier reported pedigrees.[15, 16] A different sex incidence may be one feature differentiating spondylitis in which there appears to be a genetic factor (completely or irregularly dominant) from "sporadic" spondylitis.

The inherited nature of this disease in some kindreds is a fact of practical importance. The condition often goes unrecognized in its early stages. This is unfortunate in view of the high degree of relief resulting from prompt roentgen-ray therapy,[41, 42, 43, 44, 45, 46] as illustrated by III 22 and 24. When the diagnosis of ankylosing spondylitis has been reached in a patient, the clinician may view with appropriate suspicion any other members of the kindred, especially siblings and children of affected persons, presenting the symptom of backache.

Summary

A pedigree is described extending over four generations and composed of 87 persons, including in generation II a sibship of 12 individuals ranging in age from 36 to 59.

Verified spondylitis rhizomelique, satisfying all the clinical requirements, is present in three persons in generation II, and in two of their five children in generation III. Three of the five affected persons are females. It is more than probable that in generation I the female progenitor of the kindred also had the disease. The individuals composing generation IV are still below the usual age of onset of the disease.

The condition appears to be transmitted in this kindred as if due to a single autosomal dominant gene whose exact frequency of expression cannot be specified at the present time. In addition to spondylitis rhizomelique, other types of arthritis are found in this family, namely, hypertrophic and "menopausal" arthritis, as well as less clearly defined entities. The possibility of an arthritis diathesis is discussed.

BIBLIOGRAPHY

1. Magnus-Levy, A.: Ueber die chronische Steifigkeit der Wirbelsäule, Mitt. Grenzgeb. Med. u. Chir. **9**: 626–658, 1902.
2. Osgood, R. B.: The medical and social approaches to the problem of chronic rheumatism, Am. J. M. Sc. **200**: 429–445, 1940.
3. Ravenna, P.: A review of recent Italian work on rheumatism. II. Chronic rheumatism, Ann. Rheumat. Dis. **2**: 1–18, 1940.
4. Hermann, R.: Über die Erblichkeit bei den Arthrosis degenerativa, Ztschr. Menschl. Vererbungs.-u. Konstitutionl. **19**: 707–720, 1936.
5. Stecher, R. M., and Hersh, A. H.: Heberden's nodes: the mechanism of inheritance of hypertrophic arthritis of the fingers, J. Clin. Investigation **23**: 699–704, 1944.
6. Talbott, J. H.: Serum urate in relatives of gouty patients, J. Clin. Investigation **19**: 645–648, 1940.

7. Smyth, C. J., and Freyberg, R. H.: A study of the hereditary nature of gout; a report of two families, Ann. Int. Med. **16**: 46–56, 1942.
8. Neel, J. V.: The clinical detection of the genetic carriers of inherited disease, Medicine **26**: 115–153, 1947.
9. Wilson, M. G., Schweitzer, M. D., and Lubschez, R.: The familial epidemiology of rheumatic fever: genetic and epidemiologic studies. I. Genetic studies, J. Pediat. **22**: 468–492, 1943.
10. Holsti, Ö., and Rantasalo, V.: On the occurrence of arthritis in Finland, Acta med. Scandinav. **88**: 180–195, 1936.
11. Holsti, Ö., and Huuskonen, A. J.: Heredo-familial arthritis, Acta med. Scandinav. Suppl. **89**: 128–138, 1938.
12. Hangarter, W.: Erbliche Disposition bei chronischer Arthritis, Ztschr. Ges. Anat. Abt. II, Ztschr. f. Konstitutionsl. **16**: 244–260, 1932.
13. Dawson, M. H., and Tyson, T. L.: The relationship between rheumatic fever and rheumatoid arthritis, Proc. Am. Ass. for Study and Control of Rheum. Dis. **2**: 132–142, 1935.
14. Coss, J. A.: Juvenile rheumatoid arthritis, M. Clin. North America **30**: 568–575, 1946.
15. Von Bechterew, W.: Steifigkeit der Wirbelsäule und ihre Verkrümmung als besondere Erkrankungsforme, Neurol. Centralbl. **12**: 426–434, 1893.
16. Marie, P., and Astié, C.: Sur un cas de cyphose hérédo-traumatique, Presse méd. **2**: 205–206, 1897.
17. Geilinger, W.: Beitrag zur Lehre von der ankylosierenden Spondylitis mit besonderer Berücksichtigung ihrer Beziehungen zur Spondylitis deformans, Z. Orthop. Chirurgie **38**: 183–269, 1918.
18. Weil, A. J., and Allolio, B.: Spondylitis ankylopoietica (Bechterew) bei Brudern, Deutsche med. Wchnschr. **56**: 2038–2039, 1930.
19. Ehrlich, C.: Die sogenannte Bechterew'sche Krankheit. Eine chronische zur Versteifung führende Erkrankung der Wirbelsäule, Berlin, R. Hobbing, 1930, pp. 58.
20. Blair, H. C.: Spondylitis adolescens—Struempell-Marie disease; practical and theoretical considerations, Surg., Gynec. and Obst. **74**: 663–670, 1942.
21. Dekkers, H. J. N.: Spondylarthritis ankylopoietica (spondylosis rhizomelica) combined with peripheral arthritis, Acta med. Scandinav. **113**: 506–526, 1943.
22. Stecher, R. M., and Hauser, H.: Ankylosing spondylitis. Report of occurrence in two brothers, Am. J. Roentgenol. **56**: 601–606, 1946.
23. Fischer, A.: Rheumatismus und Grenzgebiete, Fachbücher f. Ärtze, Berlin, Julius Springer, 1933, xv, pp. vi and 223.
24. Herrick, W. W., and Tyson, T. L.: Medical aspect of ankylosing spondylitis (Marie-Strümpell), Ann. Int. Med. **15**: 994–1001, 1941.
25. Claussen, F., and Kober, E.: Über die Veranlagung zu Bechterewscher Krankheit und ihr Wesen, Ztschr. f. menschl. Vererb.- u. Konstitutionsl. **22**: 268–303, 1939.
26. Comroe, B. I.: Arthritis and allied conditions, 1944, Lea and Febiger, Philadelphia, p. 1359.
27. Stephens, F. E., and Kerby, J. P.: Hereditary Legg-Calve-Perthe's disease, J. Hered. **37**: 153–160, 1946.
28. Gill, A. B.: Relationship of Legg-Perthe's disease to the function of the thyroid gland, J. Bone and Joint Surg. **25**: 892–901, 1943.
29. Levy, L. J., and Girard, P. M.: Legg-Perthe's disease, J. Bone and Joint Surg. **24**: 663–671, 1942.
30. Bauer, J.: Constitution and disease, 1945, Grune and Stratton, New York, pp. xiii and 247.
31. Draper, G., Allen, G., and Spock, J. C.: Studies in human constitution. VI. Clinical genetics, J. A. M. A. **92**: 2149–2153, 1929.
32. Proebster, R.: Bemerkungen zum chronischen Gelenkrheumatismus an Hand einiger Fälle von rheumatischer Erkrankung der kleinen Wirbelgelenke, Arch. f. orthop. u. Unfall-Chir. **21**: 346–385, 1923.

33. Miller, J. L.: Differential diagnosis between Strümpell-Marie disease and osteoarthritis of the spine, J. Lab. and Clin. Med. **22**: 19–25, 1936.
34. Kinsella, R. A.: Differential diagnosis of acute rheumatic fever, J. Lab. and Clin. Med. **22**: 26–29, 1936.
35. Pottenger, R. T.: Constitutional factors in arthritis with special reference to incidence and role of allergic diseases, Ann. Int. Med. **12**: 323–333 (Sept.) 1938.
36. Reed, S. C.: Harelip in the house mouse. I. Effects of the external and internal environments, Genetics **21**: 339–360, 1936.
37. Pearson, E. S.: Congenital eye anomalies in albino mice, Nature, London **114**: 433, 1924.
38. Loeffler, L.: Über eine mutation bei der weissen Hausmans, ihre Genetik und deren Bedeutung für die menschliche Erblehre, Z. i. Abst. Vererb. **61**: 409–446, 1932.
39. Danforth, C. H.: Hereditary doubling suggesting anomalous chromatin distribution in the mouse, Proc. Soc. Exper. Biol. and Med. **23**: 145–147, 1925.
40. Polley, H. F., and Slocumb, C. H.: Rheumatoid spondylitis; a study of 1,035 cases, Ann. Int. Med. **26**: 240–249, 1947.
41. Kemen, A.: Röntgenbehandlung der rheumatischen Erkrankungen ins besondere der Bechterewschen Erkrankung, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **49**: (Deutsche Gesellsch. f. Rheumabe Kämpf.) 46–54, 1937.
42. Scott, S. G.: Wide field x-ray treatment, 1939, George Newnes, Ltd., London, pp. xiv and 80.
43. Hare, H. F.: The diagnosis of Marie-Strümpell arthritis with certain aspects of treatment, New England J. Med. **223**: 702–705, 1940.
44. Smyth, C. J., Freyberg, R. H., and Lampe, I.: Roentgen therapy for rheumatoid arthritis of the spine, J. A. M. A. **117**: 826–831, 1941.
45. Smith, R. T., Boland, E. W., and Hench, P. S.: The effect of roentgen therapy in rheumatoid spondylitis, Read before American Rheumatism Assn., New York City, May 25, 1946.
46. Freyberg, R. H.: Roentgen therapy for rheumatic disease, M. Clin. North America **30**: 603–615, 1946.

CASE REPORTS

FRANK HEMATURIA AS A MANIFESTATION OF INFECTIOUS MONONUCLEOSIS *

By W. T. Thompson, Jr., M.D., and Cullen Pitt, M.D., *Richmond, Virginia*

That the urinary tract can be involved during the course of infectious mononucleosis is an established fact. However, this is not a frequent or generally recognized complication. Tidy and Morley [1] reported an incidence of 6 per cent in 270 cases analyzed in 1921, and Wechsler [2] found abnormal urinary manifestations in 3 per cent of 556 cases observed during an army epidemic. This 3 per cent included those cases showing red and white blood cells, albumin, and hyaline and granular casts. He referred to two cases of frank hematuria. Many series of cases reported in the literature over a period of years either made no mention of renal changes or stated that none was noted. This case of infectious mononucleosis is presented to call attention to the fact that frank hematuria may be an outstanding feature of the disease.

Case Report

An 18 year old college girl developed lower abdominal dull aching pain and general malaise on January 4, 1948. On January 7 she felt feverish, had a sore throat, and noted tender swellings behind her right ear and along both sides of her neck. On this day laboratory studies were done which established the diagnosis of infectious mononucleosis. The hemoglobin was 88 per cent, white blood cells 20,800, polynuclear neutrophiles 11 per cent, round cells characteristic of infectious mononucleosis 83 per cent, and large mononuclear cells 6 per cent. The urine was amber, slightly cloudy, acid; specific gravity 1.015, with a distinct trace of albumin; sugar and acetone negative, bile present. Microscopic examination of the urinary sediment showed 6 to 10 red blood cells per high power field, 10 to 12 white blood cells per high power field, and no casts. Heterophil agglutination was positive in a dilution higher than 1:1,024. Blood Eagle test was negative.

On the morning of January 10, the patient noticed grossly red urine. She had some frequency which she attributed to forcing fluids, but no dysuria, nocturia, or pain. Because she continued to pass grossly bloody urine she was hospitalized on January 11 for observation and study.

Her history was otherwise negative. She had anorexia and tendency to constipation with the present illness.

Physical examination revealed a well developed, well nourished young woman, acutely but not seriously ill. Her temperature was 100.8° F., pulse 104, and blood pressure 124/82 mm. Hg. Her tonsils were absent; her throat was injected. There was a generalized lymphadenopathy with most marked involvement of the posterior cervical chains. Lungs were clear. The heart was normal in size and shape, rate rapid, regular, sounds of good quality. There was a short systolic murmur heard

* Received for publication September 18, 1948.
From the Medical Service of St. Luke's Hospital, Richmond, Va.

over the precordium, best at the pulmonic area. No abnormal organs or masses were palpable but there was slight tenderness in the right upper quadrant.

Roentgen-ray of the chest and an electrocardiogram were normal.

Laboratory studies on admission to the hospital showed hemoglobin 84 per cent, white blood cells 10,900, polynuclear neutrophiles 15 per cent, leukocytoid type of lymphocyte characteristic of infectious mononucleosis 81 per cent, large mononuclear cells 4 per cent. Platelets were normal on the stained blood smear. Urine was grossly red, cloudy, acid, specific gravity 1.010, abundant albumin, no sugar or acetone. Microscopic examination of sediment showed innumerable red blood cells. A specimen examined the next day was also grossly bloody and showed the same findings.

Course in Hospital: Her temperature ranged from normal to 101° until January 16, when it remained normal. She was given only symptomatic remedies and remained fairly comfortable. In spite of the fact that the diagnosis of infectious mononucleosis had been established, because of the persistence of grossly bloody urine she was cystoscoped January 12. The bladder was normal, and cloudy urine was seen to spurt from both ureteral orifices. Urine examined the next day was not grossly bloody, was amber, acid; specific gravity 1.010; distinct trace of albumin; sugar and acetone negative. Sediment showed numerous red blood cells and occasional pus cells.

She passed no more bloody urine. On January 16 she felt much better, her temperature was normal, and she was discharged. Heterophile agglutination was positive 1:2,048. Urinalysis on discharge showed amber color, acid reaction, specific gravity 1.018, trace of albumin. The sediment showed no red blood cells and only 1 to 5 pus cells per high power field. Urinalysis done a month after discharge was completely negative, and the patient has remained well in every way.

SUMMARY

A case of infectious mononucleosis has been presented which emphasizes the fact that renal changes do occur in this disease, and that frank hematuria may be a part of the clinical picture.

BIBLIOGRAPHY

1. Tidy, H. L., and Morley, E. B.: Glandular fever, Brit. M. J. 1: 452 (March 26) 1921.
2. Wechsler, H. F., Rosenblum, A. H., and Sills, C. T.: Infectious mononucleosis: report of epidemic in army post, Ann. Int. Med: 25: 113 (July) 1946; Part II, Ann. Int. Med. 25: 236 (August) 1946.

IDIOPATHIC THROMBOPHLEBITIS MIGRANS WITH UNUSUAL MANIFESTATIONS *

By PHILIP M. GOTTLIEB, M.D., DAVID TURNOFF, M.D., JOSEPH J. ZIMMERMAN, M.D., and WILLIAM D. CHAMBLIN, M.D., *Philadelphia, Pennsylvania*

IDIOPATHIC thrombophlebitis migrans is relatively uncommon. Swirsky and Cassano [1] in 1943 found 100 cases with only four autopsy reports in the literature. In a later review, Fischer [2] in 1946 found a total of 114 cases, including six which

* Received for publication September 16, 1948.
From the medical service of Dr. Truman G. Schnabel, Philadelphia General Hospital, Philadelphia, Pennsylvania.

he reported. Approximately 40 per cent of patients with thromboangiitis obliterans present a superficial thrombophlebitis at some time during the course of the disease.[3] Other instances of thrombophlebitis associated with systemic disease (scarlet fever,[4] pneumonia,[5] frostbite,[6] and the like) are also well identified.

The following case seems to be an example of a primary thrombophlebitic process affecting the veins without evidence of concurrent disease. The associated clinical manifestations are unique and considered worth reporting.

Case Report

A 31 year old Negro was admitted to the Philadelphia General Hospital on April 10, 1947, with chief complaints of fever and pain in the right anterior portion of the chest. Productive cough had been present for two weeks, and chills and high fever for three days. The pain was aggravated by deep breathing, movement, or cough. Increasingly severe dyspnea was noted.

In addition, the patient complained of chronic painless swelling of all extremities. He stated that at the age of 13 years, while he was living in Fitzgerald, Georgia (where he was born), he had had an acute febrile illness accompanied by tender, red, hard streaks in the left calf, with slight swelling and considerable pain. Shortly following this, persistent swelling appeared in the left lower extremity. Between the ages of 13 and 17 years, he had four bouts of unexplained fever ranging up to 40° C. (104° F.), each lasting one to two weeks and unaccompanied by pain. At the age of 17 years he had similar involvement of the right leg, with radiation of the pain to the right thigh and into the lower abdomen. Thereafter, the right leg was swollen. He has had no fever, pain, or acute episodes in the lower extremities since that time. In 1941, swelling of the left arm was noted for the first time, and within two weeks the right arm was affected. The upper extremity involvement has subsided from time to time, but has followed an irregularly progressive course.

The swelling is considerably reduced after a period of recumbency. However, the lower extremities have at no time returned to normal since the onset. There has been no difficulty in walking, working as a laborer, or in cold weather. Paresthesias, bleeding tendencies, and weakness were denied. On two occasions, ulceration in the region of the ankles appeared after slight trauma.

In 1941, skin grafting had been successfully performed on a large ulcer on the left leg and a mixed tumor of the left parotid gland removed.

The patient was studied in 1944 at another local hospital. Lymphedema of all four extremities was present at that time. Each venipuncture precipitated an acute local thrombophlebitis. Hydrothorax as well as swelling of the abdominal and thoracic walls apparently occurred for the first time following his discharge, leading to his re-admission to the same hospital three weeks later. Several thoracenteses on each side yielded large amounts of straw-colored fluid containing 182 to 550 leukocytes per cubic millimeter and 3.0 to 3.7 gm. of protein per 100 ml. Aerobic and anaerobic cultures were sterile, and guinea pig inoculations were negative for *Mycobacterium tuberculosis*. Dicumarol and heparin therapy were instituted because of phlebitis of the left arm. After search for focal infection, tonsillectomy was performed without apparent benefit. The patient was discharged improved following several injections of Mercupurin (Mercuzanthin) and the application of elastic bandages to the lower extremities. Other significant findings at that time included absent ulnar pulses, thrombosed superficial veins of the right calf and both arms, reduced oscillometric readings at both ankles, and roentgen evidence of thickened pleura at both bases, with varying amounts of pleural effusion bilaterally. An attempted venogram on the right leg was unsuccessful because a sufficient amount of the contrast medium

could not be introduced into the vein. Biopsy of a thrombosed left cephalic vein (figure 1) revealed the lumen to be incompletely occluded by cellular proliferation, fibrous tissue, new vessels, and erythrocytes. Scattered inflammatory cells, predominantly small monocytes, infiltrated the mass in the lumen and adjacent intima with little change in the surrounding vein wall. The histologic impression was that of an ordinary organizing and recanalizing thrombus, possibly compatible with thromboangiitis obliterans. Numerous urinalyses were within normal limits, as were repeated blood urea nitrogen, carbon dioxide combining power, chloride and protein determinations. There was no anemia. The leukocyte count varied between 8,500

FIG. 1 *A*. Section of thrombosed cephalic vein (low power).

FIG. 1 *B*. Section of adherent thrombus (high power).

and 11,650 per cu. mm., with a normal differential count. Serologic tests for syphilis were repeatedly negative. Basal metabolic rate was minus 21. Microfilaria were not found in several blood specimens taken during both the day and the night.

The past medical history was otherwise noncontributory as were the social history and the family history. No similar conditions were known in any relative or contact. The patient has never been outside the United States.

Physical examination on the first admission to this hospital (April, 1947) revealed a well-developed, acutely ill, febrile, markedly dyspneic Negro male. The temperature was 40° C. (104° F.). The blood pressure was 150 mm. of mercury sys-

tolic, 80 mm. diastolic. There was marked enlargement of both lower extremities to about twice their normal size, with firm, nontender, nonpitting, brawny edema (figure 2). The overlying skin was thickened, irregular, nodular, and typically elephantiasic. The dorsa of both hands and adjacent portions of both forearms were the sites of somewhat softer and less extensive swelling. Edema of the penis was present. Keloidal scars on the left leg and lower abdomen represented the recipient and donor sites of the previous skin grafting. No significant lymphadenopathy was noted. Signs of hydrothorax were detected over the lower half of the right chest, with displacement of the trachea and apex beat to the left. Complete neurologic examination was negative. The pleural effusion was confirmed roentgenographically

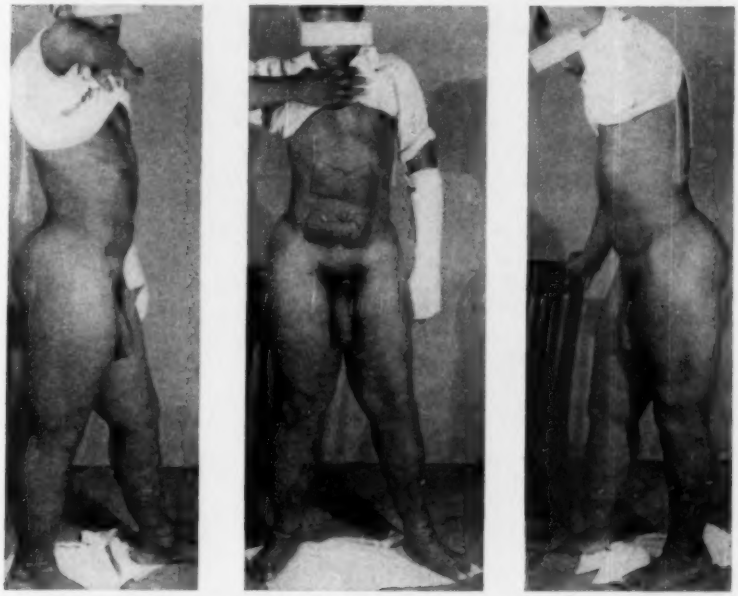


FIG. 2. Photograph of patient illustrating extent of lymphedema. Note elephantiasis of lower extremities and areas of skin grafting. Penis is edematous. The edema of the upper extremities is not clearly shown.

(figure 3A), and on the second day of hospitalization about 1,900 c.c. of cloudy, yellow, fairly viscous fluid were removed by thoracentesis. On successive days, 1,500 and 1,200 c.c. of similar fluid were removed, and 200,000 units of penicillin instilled into the pleural cavity. A total of seven more thoracenteses, yielding quantities varying from 500 to 1,000 c.c., were performed at intervals of two to six, and finally 10 days. The last few taps were somewhat sanguineous.

Roentgenologic reëxamination promptly after the seventh tap (figure 3B) revealed a small right hydropneumothorax and markedly thickened visceral and parietal pleura on this side. The left lung was normal. The swelling of legs subsided greatly but did not disappear after two or three days of bed rest. The patient was given 50,000 units of penicillin intramuscularly every three hours for 10 days, and sulfadiazine

for 19 days. He became afebrile in seven days and was improved on discharge on May 23, 1947.

He was followed at bi-weekly intervals in the Medical Out-Patient Department and was subjected to three more thoracenteses before his readmission on August 7, 1947, to the Medical Ward, where he remained for 23 days. At this time he was essentially afebrile and his only complaint was dyspnea on moderate exertion. The findings were virtually the same as on previous admission, with evidence of moderate

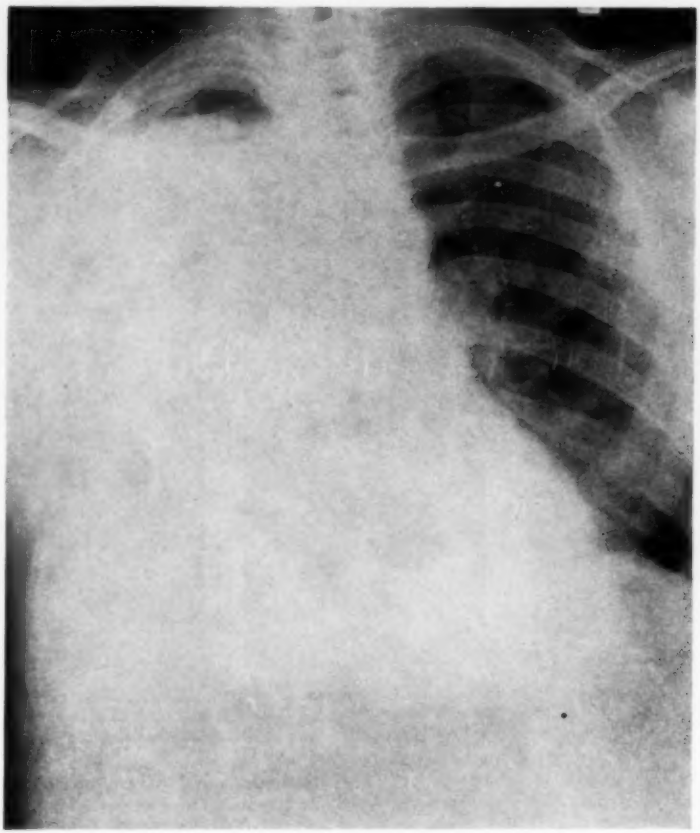


FIG. 3 *A*. Roentgenogram of chest on admission.

pleural fluid on the right. There was now considerable nonpitting swelling of the scrotum and penis in addition to the involvement of the extremities. Thoracentesis twice yielded clear orange-red fluid. Each venipuncture for test or the introduction of diagnostic material was followed by an afebrile phlebitis of the arm vein employed. This subsided each time in a few days with rest, hot wet dressings, and pressure bandages.

Following this hospitalization, the patient was able to perform successfully the duties of night orderly on the wards. His last admission, from March 17 to 22, 1948, was for further study while he was asymptomatic. Biopsy of skin and subcutaneous tissues (figure 4) at this time revealed edema and marked distention of small lymph vessels, as well as some perivascular round cell infiltration.

Other findings during the past 11 months, during three hospitalizations and intervening out-patient department observation, were as follows: Numerous chest

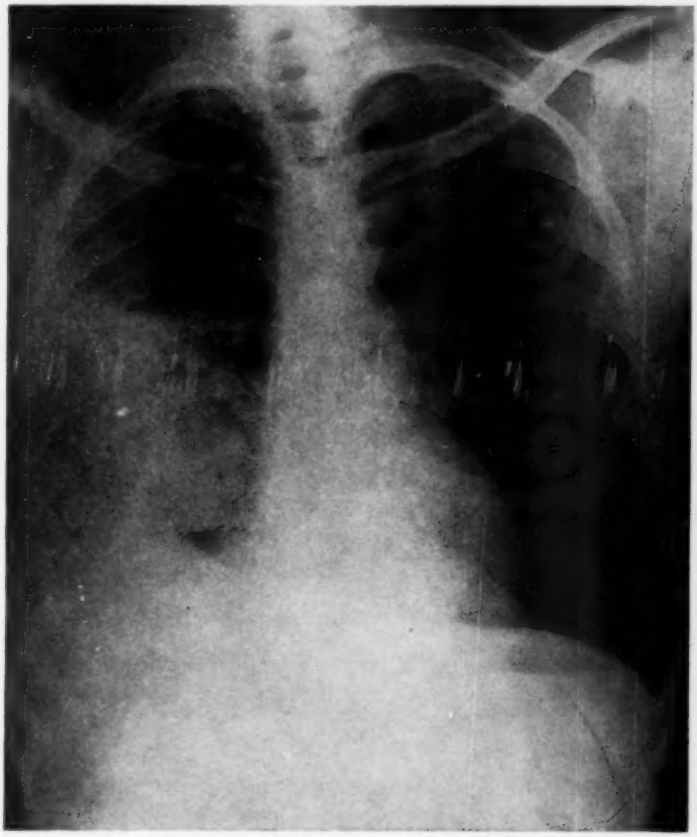


FIG. 3 *B*. Roentgenogram of chest after thoracenteses.

roentgen-ray films revealed only thickening of the visceral and parietal pleura at both bases, varying amounts of right hydrothorax or hydropneumothorax, depending in part on the prior withdrawal of fluid by paracentesis. Parenchymal lesions of the lungs were never demonstrated. The sputum was repeatedly negative for acid-fast bacilli, as was a gastric washing. Sputum culture revealed pneumococci, *Streptococcus viridans*, and *Neisseria catarrhalis*. The pleural effusions on nine occasions were

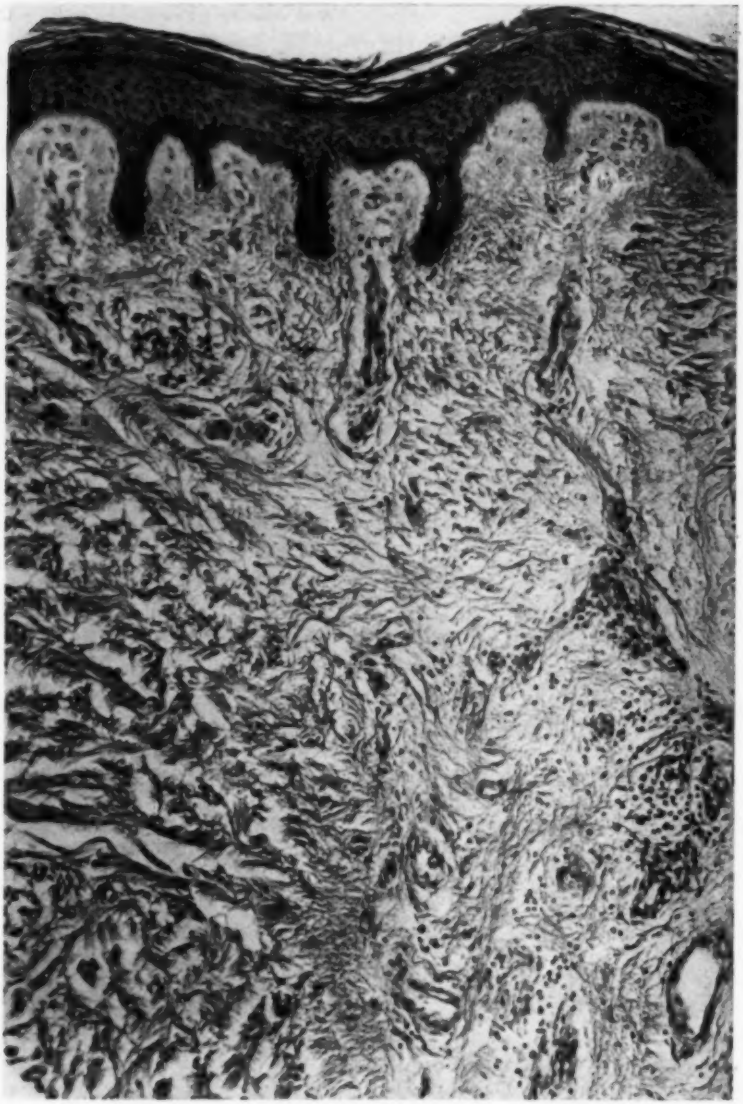


FIG. 4. Biopsy of skin and subcutaneous tissues (high power).

negative for acid-fast bacilli and sterile on culture, including the use of special mediums for tubercle bacilli. Its specific gravity varied from 1.016 to 1.022, with 90 to 640 leukocytes, of which 59 to 99 per cent were polymorphonuclears and the remainder lymphocytes. On chemical analysis, 4.8 per cent of protein and 18 mg.

per 100 c.c. of sugar were found on two occasions. Histologic study of paraffin block sections of the sediment revealed an inflammatory exudate free of acid-fast bacilli and malignant cells.

Blood count: hemoglobin, 11.5 to 13.1 gm. per 100 c.c.; erythrocytes, 3.5 to 3.68 million per cu. mm.; leukocytes, 5,400 to 6,200, with 65 to 76 per cent polymorphonuclears, 60 to 31 per cent lymphocytes, 3 to 6 per cent monocytes, and 1 to 2 per cent eosinophiles. Slight achromia was noted. There was no sickling on special preparation. Platelets were 248,000 per cu. mm., bleeding time 55 and 108 seconds, and clotting time 4.5 and 3.5 minutes. Clot retraction began in one hour. Erythrocyte sedimentation rate (Cutler) was 16 mm. in one hour. Urinalyses were within normal limits except for traces of albumin increasing to 1 to 3 plus at times, and varying numbers of leukocytes. The Kahn and Kline tests were repeatedly negative. The stools were free from ova, parasites, and occult blood.

The blood sugar was 89 and 84, urea nitrogen 11 and 14, cholesterol 121, bilirubin 0.47, calcium 10.3, and phosphorus 3.5 mg. per 100 c.c. The blood proteins were 7.5 and 8.1 per cent, with albumin 4.5 and 4.8, and globulin 3.0 and 3.3 per cent. The prothrombin time was 45 per cent of normal. The thymol turbidity was 2.5 units; thymol and cephalin flocculations were negative. The Congo red test showed 10 and 35 per cent absorption at the end of one hour on two tests. Edema fluid from the leg contained 0.7 per cent of protein.

The Frei test was twice negative. The circulation time, arm-to-tongue, with calcium gluconate was 19.0 seconds, and with strontium bromide 15.2 seconds. Venous pressure in a dilated right saphenous vein was 9.9 cm. of water.

Discussion

In summary, this is a 31 year old patient who, after repeated thrombophlebitic episodes for a period of 18 years, presents lymphedema of all four extremities, the abdominal wall, penis and scrotum, and recurrent massive pleural effusions. There seems little evidence for a diagnosis other than thrombophlebitis migrans. Although the venous pathology in thromboangiitis obliterans and thrombophlebitis migrans is indistinguishable,[7] there are no clinical signs of arterial circulatory impairment in the extremities after 13 years. However, this cannot be entirely excluded as a future possibility.[8] Further, lymphedema is not reported as a manifestation or complication of Buerger's disease.[8] Search for some abnormal clotting mechanism in the blood proved unrevealing. No filaria were found, nor could any other infectious agent be identified as a possible etiologic factor. Although the edema, low basal metabolic rate, and the intermittent proteinuria suggest the nephrotic syndrome, the serum proteins and cholesterol are normal and the course is quite unusual for primary renal disease. This is not myxedema. While this patient presents a striking picture because of the manifest swelling of his extremities, the diagnosis of primary lymphedema is untenable by virtue of the major rôle of the thrombophlebitic phenomena. The clinical course, protean manifestations, biopsy studies, and examination of the edema fluid are all compatible with a diagnosis of an idiopathic migrating thrombophlebitis with secondary inflammatory lymphatic obstruction and lymphedema.

This patient presents involvement of all four extremities, penis and scrotum, superficial veins of the trunk, and intrathoracic veins. This is very extensive. In the great majority of reported cases, involvement is confined to the extremities.[2, 7] However, in rare instances the mesenteric veins,[9, 10] veins of the heart,[10] the breast,[11] and those of the brain [12] have also been involved.

Fischer [2] collected 23 examples of pulmonary involvement and agrees with Barker [7] that these are most likely examples of pulmonary infarction rather than pulmonary thrombophlebitis. Studies of small pleural effusions in other cases [1, 10, 13] of thrombophlebitis migrans revealed serosanguineous, sterile fluid. The clinical course seemed typical of pulmonary infarction, and two autopsy reports corroborated this impression.[1, 14] No examples of recurrent serous effusions of such magnitude as exhibited by this patient were found in the literature. In the absence of clinical and roentgenographic evidence for pulmonary infarction, we feel it is reasonable to deduce that in the present case the pulmonic and perhaps other intrathoracic veins are involved in this same thrombophlebitic process.

Summary

A case is reported of thrombophlebitis migrans with extensive lymphedema and recurrent, massive pleural effusions. All four extremities, the penis, scrotum, and trunk were involved in the thrombophlebitic process and lymphedema.

BIBLIOGRAPHY

1. Swirsky, M. Y., and Cassano, C.: Thrombophlebitis migrans, J. Lab. and Clin. Med. **28**: 1812–1816 (Dec.) 1943.
2. Fischer, E. H.: Thrombophlebitis migrans, J. Kansas M. Soc. **47**: 245–249 (June) 1946.
3. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral vascular diseases, 1947, W. B. Saunders Company, Philadelphia.
4. Bates, J. V.: Post-scarlatinal thrombophlebitis migrans, Brit. M. J. **1**: 665 (May 29) 1943.
5. Ficarra, B. J.: Migratory polyphlebitis, Arch. Surg. **53**: 105–110 (July) 1946.
6. Van Langenberg, E. R.: Phlebitis migrans, J. Roy. Nav. M. Serv. **28**: 392–393 (Oct.) 1942.
7. Barker, N. W.: Recurrent idiopathic thrombophlebitis, Proc. Staff Meet., Mayo Clin. **10**: 373–375 (June 12) 1935.
8. d'Abreu, A. L.: Relation of thrombophlebitis migrans to thromboangiitis obliterans, Brit. M. J. **1**: 101–102 (Jan.) 1934.
9. Birnberg, V. J., and Hansen, A. E.: Thrombophlebitis migrans, J. Pediat. **21**: 775–786 (Dec.) 1942.
10. Moorhead, T. G., and Abrahamson, L.: Thrombophlebitis migrans, Brit. M. J. **1**: 586–587 (Apr. 7) 1928.
11. Flood, E. P., Reddish, M. H., Bociek, S. J., and Shapiro, S.: Thrombophlebitis migrans disseminata: case in which gangrene of the breast occurred, New York State J. Med. **43**: 1121–1124 (June 15) 1943.
12. Bucy, P. C., and Lesemann, F. J.: Idiopathic recurrent thrombophlebitis with cerebral venous thrombosis and acute subdural hematoma, J. A. M. A. **119**: 402–405 (May 30) 1942.
13. Ryle, J. A.: Thrombophlebitis migrans, Lancet **2**: 731–733 (Oct. 4) 1930.
14. Hirschborn, L., Lisa, J. R., and Goldstein, R. J.: Thrombophlebitis migrans: case report, Am. Heart J. **17**: 76–84 (Jan.) 1939.

NEUTROPENIA IN A PATIENT TREATED WITH A MERCURIAL DIURETIC AND ITS RESPONSE TO BAL *

By CHARLES E. BENDER, M.D., ROBERT J. HOXSEY, M.D., and QUIN B. DEMARSH, M.D., *Seattle, Washington*

A REVIEW of the causes of agranulocytosis and the neutropenic states has revealed no case in which an organic mercurial diuretic was suspected as the etiologic agent.

In the case being reported, a 61 year old white woman, a known hypertensive for six years, was given Mercupurin 2 c.c. intravenously three times weekly for 38 weeks, followed by the same dose daily for 14 days. On admission the white blood count was 1,000 per cu. mm., the differential showed polymorphonuclears 5, lymphocytes 57, monocytes 30, eosinophil 1, basophils 3, unclassified 4. A course of BAL was administered, and a count taken on the same day on which the last dose of BAL was given showed white blood count 7,200 per cu. mm., with polymorphonuclears 89, lymphocytes 5, monocytes 4, basophils 2. Myelograms taken on the day preceding and the day following completion of treatment strongly suggest that the mercurial may have been responsible for the granulocytopenia.

CASE REPORT

A 61 year old white woman was admitted to King County Hospital for the third time on October 21, 1947, because of prostration, dyspnea and anasarca of 10 months' duration.

Past Medical History: Patient had usual childhood diseases, with typhoid fever at 17 years, bilateral salpingectomy and unilateral oöphorectomy and appendectomy at 27 years. A "nervous breakdown" over a marital conflict at 54 years. Para ii, gravida iii.

Family history revealed that a grandmother died as a result of hypertension; and that the patient's mother died of arteriosclerotic heart disease. The patient was followed by her own physician during 1943, at which time her weight was 180 pounds, blood pressure 214/110 mm. Hg. White blood count, 9,900 per cu. mm. The urine was negative for albumin and reducing substances, and the Fishberg concentration test showed specific gravities 1.022, 1.021, 1.015.

First admission to King County Hospital, July 19, 1946. The chief complaint was edema and shortness of breath. These had been present since April, 1946, following the primary take of a vaccination. Because of weakness, most of the year prior to admission had been spent in bed. She was admitted to a local hospital because of coma in June, 1946, where she remained a week. Her physician was administering thiocyanates, morphine sulfate and digitalis at this time.

The blood pressure on admission was 260/120. Funduscopic examination revealed hazy discs, venous engorgement, reduced arterial caliber, and old and new exudates. Laboratory findings: Urinalysis: specific gravity 1.005, 75 mg. albumin per 100 c.c., Fishberg specific gravities 1.014-quantity insufficient-1.015. Phenolsulfonphthalein excretion less than 10 per cent in two hours. Total blood proteins, 6.2 gm. Blood urea nitrogen 19 mg. per cent. Venous pressure 130 mm. saline. Arm-to-tongue decholin circulation time, 13 seconds. Thiocyanates, 3.2 mg. per cent.

* Received for publication July 15, 1948.

From the Department of Medicine, University of Washington School of Medicine and King County Hospital, Seattle, Washington.

A retrograde pyelogram showed blunted calyces on the right and possible narrowing of the right upper ureter. Dye appeared in six minutes on the left but not after 30 minutes on the right. The patient was discharged on September 27, 1946, with blood pressure 220/140 and diagnosis of hypertensive vascular disease and nephrosclerosis.

Second admission, December 2, 1946. She returned because of severe dyspnea. The physical examination was the same except for bilateral cervical adenopathy and questionable enlargement of the right lobe of the thyroid. Blood pressure 220/140, heart rate 88 and regular. Moist râles were present at both bases. The liver was down 2 cm. below the costal margin; there was no peripheral edema. A chest radiograph showed aortic configuration of the heart and a small amount of left pleural fluid. Laboratory: 100 mg. albumin per 100 c.c. urine, Fishberg specific gravities 1.007–1.009–1.008, 12 granular and 3 hyalin casts per high power field. Phenolsulfonphthalein excretion less than 10 per cent in two hours. Blood cholesterol, 236 mg. per cent. She was discharged on December 13, on a salt poor diet, phenobarbital and aminophylline.

Last admission, October 21, 1947. The chief complaint was prostration, dyspnea and anasarca of 10 months' duration; following previous discharge, most of her time was spent in bed. For the past nine and a half months she had received Mercupurin 2 c.c. intravenously three times weekly, and then 2 c.c. nightly for the past two weeks.

TABLE I

Blood Counts before and after BAL

	Hb.	RBC	WBC	P	L	M	E	B	Uncl.
7-15-1943			9,900						
7-19-1946	9.4		2,500	68	26	4	2		
12-9-1946	10.2	3.3	6,500						
10-21-1947	10.8	3.8	1,000	5	57	30	1	3	4
10-24-1947*			900	5	12	82	1		
10-29-1947	BAL 150 mg. 75 mg. 75 mg.								
30	BAL 75 mg. 75 mg.								
31	BAL 75 mg. 75 mg.								
11-1-1947	BAL 75 mg.								
2	BAL 75 mg.								
11-2-1947	10.05	3.92	7,200	89	5	4		2	
3			7,000	91	9				
7			6,300	86	10	4			
10			5,500	62	30	3	3	2	
11-14-1947	7.05	2.68	4,200	69	21	8	2		
1-14-1948			4,100	63	19	15	2	1	

* Monocytes and neutrophils on 10-24-1947 were loaded with toxic granules.

She was given 15 mg. morphine sulfate once or twice weekly. The patient appeared both chronically and acutely ill; she was dyspneic but not cyanotic. Lethargy was apparent. The temperature was 37.9° Centigrade and blood pressure 160/80. The eyegrounds showed advanced retinopathy. There was a large excoriated area inside the left ala nasi which was covered with crusted blood. The jaws were edentulous and the pharynx was moderately injected. Dullness was present over the lower third of both lungs posteriorly, fremitus was decreased to absent, and crepitant râles were numerous in the same areas. The left heart border was 12 cm. from the midsternal line in the sixth interspace, the rate was 90 and irregular, and a Grade I aortic systolic murmur was present. The liver was down 5 cm., and there was slight sacral edema. The skin had a buckwheat pallor and there was a peculiar wide transverse orange-red band across each fingernail. A chest roentgen-ray showed the cardiac shadow enlarged to the left, increased pulmonary markings, and fluid in the left costophrenic sinus. The electrocardiogram revealed low voltage and left axis shift. The venous pressure was 230 mm. saline, arm to lung circulation time six seconds, and arm to tongue 15 seconds. Urine specific gravity, 1.011, with 150 mg. albumin per 100 c.c. Blood urea nitrogen 65 mg. per cent. Serum albumin 3.6 gm. and globulin 2.15 gm. Blood cholesterol 106 mg. per cent.

TABLE II

Bone Marrow Counts before and after BAL

	Oct. 28	Nov. 3
No cells counted	500	500
Myeloblasts	2.8	0
Promyelocytes	22.2	6
Myelocytes	10.8	12.8
Metamyelocytes	9.6	26.6
Bands	5.4	24.2
Segmenters	1.8	7
Eosinophils	1.4	2.2
Lymphocytes	1.2	2.8
Baso. normoblasts	5.8	2.4
Poly. normoblasts	18	5.6
Ortho. normoblasts	21	10.4

Initial treatment consisted of intravenous digitalization, low salt diet and bed rest. On October 23, the temperature was 39° Centigrade and pulse 100. The lung findings had cleared markedly and the liver decreased in size. The blood pressure was 218/60. Digitalization was maintained by 100 mg. of whole leaf by mouth daily. On October 26 the temperature was 36.4° Centigrade and blood pressure 230/62. Blood studies showed leukopenia and neutropenia, and sternal marrow examination a marked maturation arrest of the myeloid series. The patient's weight was 126 pounds. BAL was administered as outlined in table 1. Beginning October 23, and continuing for two weeks, she was given daily injections intramuscularly 2 c.c. of a preparation containing B_1 10 mg.; B_2 4 mg., and nicotinamide 200 mg. per c.c. A blood specimen examined spectroscopically was negative for methemoglobin. Platelet count on November 3, 1947, was 152,900 and on November 18, 1947, 131,400, with bleeding time two minutes and clotting time two and one-quarter minutes. The prothrombin time, 90 per cent of normal. Bromsulfalein (5 mg. per kilogram of body weight) showed less than 3 per cent retention after 45 minutes. The one minute bilirubin, 0.48 mg., and total, 0.95 mg. The creatinine 4.3 mg. per cent and phenol 2.09 mg. per cent. The blood counts and marrow studies after BAL are depicted in tables 1 and 2. The patient showed little improvement clinically, the marked weakness and moderate dyspnea persisting. Subsequently the liver could not be palpated and she was able to sit up in a wheel chair for short periods. Attempts to improve her

nutritional status were generally unavailing because of anorexia, especially for proteins. The blood urea nitrogen varied from 76 to 43 mg. per cent over the period from November 2 to December 2, 1947 (nine determinations). Transfusions of 250 c.c. whole blood were given on two occasions following slight melena. The temperature remained normal and she was discharged to a nursing home on December 31, 1947. Here Salyrgan-Theophylline 2 c.c. twice weekly was started January 3, 1948, because of rapidly forming edema. She died February 21, 1948.

Autopsy was done 40 hours post mortem on arterially embalmed body. Significant gross abnormalities consisted of 1,000 c.c. of yellowish fluid in peritoneal cavity and the same amount in each pleural cavity. The aorta was rough and wrinkled with numerous ragged friable plaques. The left ventricle was moderately thickened. The right kidney was small, 7 by 4 by 2.5 cm.; the left, 9 by 5 by 3 cm. Surfaces were roughly granular, and capsules stripped with some difficulty. On section, the right kidney was pale and the cortex thin. Cortex of left kidney was thin but the parenchyma was a more normal color.

Microscopic: In sections of the small right kidney, practically all glomeruli were hyalinized, and there were corresponding atrophy and shrinkage of the tubular parenchyma. In sections of the right kidney, there was much sclerosis in the large and medium sized arteries. A few glomeruli were hyalinized; some nephrons were collapsed and atrophic, some abnormally distended. There was slight periglomerular fibrosis around surviving functioning glomeruli, but otherwise they were without noteworthy change. In general, the impression was that of advanced arteriosclerotic change without evidence of active nephritis.

Discussion

When the relation of drug therapy to neutropenic states was reviewed 10 years ago, approximately 80 per cent of drug-produced agranulocytosis was caused by amidopyrine or one of its compounds.[1] Later the sulfonamides and thiouracil were recognized as drugs requiring constant alertness on the part of the physician using them. No attempt will be made to list the agents responsible for isolated cases; however, a recent report of a patient being treated for leprosy incriminates diasone as the etiologic agent and cause of death from agranulocytic angina.[2]

In patients with cardiac edema, mercurial diuretics are a valuable means of mobilizing fluids, frequently indispensable. Numerous toxic reactions are well recognized,[3, 4, 5] but no report has been found describing neutropenia and marked maturation arrest as observed in this patient.

Cases of chronic and cyclic granulocytopenia have been described[6, 7]; however, remissions in these cases seem to be characterized by gradual improvement. Agranulocytic angina manifested by recurrences at the time of the menstrual cycle are known to occur. In this patient, the menopause had occurred 15 years previously.

It is significant that for months prior to the onset of the neutropenic state the only drugs being used were Mercupurin and infrequent doses of morphine sulfate. Medications used at the time of improvement of the hematologic picture consisted of BAL, digitalis, and a vitamin B complex mixture. Pyridoxine in some instances has been given credit for the improvement observed in agranulocytic angina, but this preparation contained none.[6, 8, 9] Anemia was found to have been present since July, 1946; this we attribute to failing renal function.

There is ample evidence that renal insufficiency, generally recognized as the principal contraindication to mercurial therapy, was present in this patient. There was some decrease in the ability of the kidneys to concentrate urine, as was indicated by the Fishberg test done as early as July, 1943. This test, repeated in July and December of 1946, showed a marked deterioration in the ability to concentrate. Moderate to marked nitrogen retention and very low phenolsulfonphthalein excretion were present throughout the course.

The exact mechanism of neutropenia in agranulocytosis is not well understood. It is usually ascribed to a direct toxic inhibition of the bone marrow or a peripheral destruction of the neutrophils on the basis of an allergic reaction. The bone marrow findings in this patient led us to believe that the diuretic agent was responsible for an inhibition of maturation of the myeloid cells. We do not believe that allergy was the mechanism in this case, since readministration of a mercurial at a later date was not accompanied by neutropenia.

When the differentials in the two marrow samples are compared, it is evident that there is a marked increase of the promyelocytes, with a diminution of the more mature forms. The second specimen reveals an essentially normal marrow.

Recently Long and Farrar [10] have reported an interesting series of experiments on the protection afforded by cysteine hydrochloride, glutathione, and BAL in mercury poisoning in animals. These workers administered LD50 of Salyrgan to mice, rabbits, and dogs until toxic symptoms were produced, as evidenced by electrocardiograms and other studies, and then injected cysteine hydrochloride, glutathione or BAL, which immediately and dramatically relieved the signs of toxicity of the drug.

Because of the beneficial effects noted by others in the treatment of arsenic and mercury poisoning [11, 12] with BAL, and the work of Long and Farrar specifically on a mercurial diuretic, we feel justified in attributing the dramatic response of this patient to the use of BAL.

This patient is reported because the findings suggest that Mercupurin may, in rare instances, be responsible for serious neutropenia.

Summary

A case is reported of neutropenia occurring in a female patient given approximately 256 c.c. of Mercupurin over a 10 month period. The striking improvement noted in both the peripheral blood and the bone marrow following the use of BAL is inconsistent with the usual concept of a spontaneous remission, and suggests that BAL may have been responsible for the improvement noted.

BIBLIOGRAPHY

1. Kracke, R. R.: Relation of drug therapy to neutropenic states, J. A. M. A. **111**: 1255–1259, 1938.
2. Faget, G. H., and Erickson, P. T.: Discussion by Johnson, H. M.: Chemotherapy of leprosy, J. A. M. A. **136**: 451–457, 1948.
3. DeGraff, A. C., and Nadler, J. E.: A review of the toxic manifestations of mercurial diuretics in man, J. A. M. A. **119**: 1006–1011, 1942.

4. Ben-Asher, S.: On the toxicity of mercurial diuretics, Ann. Int. Med. **25**: 711–724, 1946.
5. Barker, M. H., Lindberg, H. A., and Thomas, M. E.: Sudden death and mercurial diuretics, J. A. M. A. **119**: 1001–1004, 1942.
6. Stealy, C. L.: Chronic granulocytopenia of five years' duration with recurrent acute attacks, Am. J. M. Sc. **189**: 633–638, 1935.
7. Stephens, D. J., and Lawrence, J. S.: Cyclic agranulocytic angina, Ann. Int. Med. **9**: 31–37, 1935.
8. Cantor, M. M., and Scott, J. W.: Agranulocytic angina effectively treated with intravenous pyridoxine, Canad. M. A. J. **52**: 368–371, 1947.
9. Moore, F. D., Discussion by Paschkis, K. E.: Toxic manifestations of thiouracil therapy, J. A. M. A. **130**: 315–319, 1946.
10. Long, W. K., and Farrar, A.: The influence of certain sulfhydryl compounds on the toxicity of an organic mercurial diuretic, J. Pharmacol. and Exper. Therap. **88**: 388–399, 1946.
11. Editorial: BAL in treatment of arsenic and mercury poisoning, Ann. Int. Med. **25**: 986–989, 1946.
12. Council on Pharmacy and Chemistry: BAL in treatment of arsenic and mercury poisoning, J. A. M. A. **131**: 824, 1946.

A CASE OF POLYCYTHEMIA VERA ASSOCIATED WITH THE WOLFF-PARKINSON-WHITE SYNDROME *

By GEORGE A. WESTFALL, JR., M.D.,† and PHYLLIS J. BURDON, M.D.,
Topeka, Kansas

ALTHOUGH the etiology of polycythemia vera remains unknown, repeated attempts have been made to correlate the condition with some cardiovascular phenomenon. Gaisböck [1] has described a syndrome characterized by polycythemia with an associated hypertension, and Reznikof, Foot and Bethea [2] have suggested an anoxia of the bone marrow as an etiologic agent. An underlying congenital cardiac defect was considered as a possible explanation for a secondary polycythemia in this case, but our studies failed to substantiate this assumption.[3]

The Wolff-Parkinson-White syndrome is characterized electrocardiographically by shortened P-R interval and aberrant QRS component. It has been shown that bouts of paroxysmal tachycardia may occur clinically in this syndrome, and also that the cardiac conduction anomaly may or may not revert to a normal rhythm when followed with serial electrocardiographic tracings.

CASE REPORT

A 27 year old white single male patient was admitted to the hospital on October 8, 1947, complaining of nervous tension, inability to concentrate, impairment of learning ability, and loss of memory.

* Presented before the Kansas State Heart Association meeting, Veterans Administration Hospital, Topeka, Kansas, on December 11, 1947. Received for publication May 8, 1948.

From the Department of Medicine, Winter Veterans Administration Hospital, Topeka, Kansas.

Sponsored by the V. A. and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

† From the Medical Department, Hertzler Clinic, formerly resident in medicine.

At the age of 13 he had had an unexplained episode of tachycardia. The diagnosis of rheumatic fever was considered at that time but was not established. Since then he had led a normal life and had taken part in athletics without symptoms referable to cardiac disease. There was no history of his having been a "blue baby." The patient had never lived at high altitudes. While in the military service all blood studies, with one exception, done at four Army hospitals revealed the hemoglobin to be 16.5 gm. or more per 100 c.c.; the red cell count was 5,500,000 cells per c.c. or higher and the white blood cell count exceeded 10,000 cells per c.c.

On physical examination the patient was found to have a third heart sound of unusual intensity. The radial pulse was 80 beats per minute and regular. The blood pressure was 140 mm. of mercury systolic and 95 mm. diastolic. There was no evi-

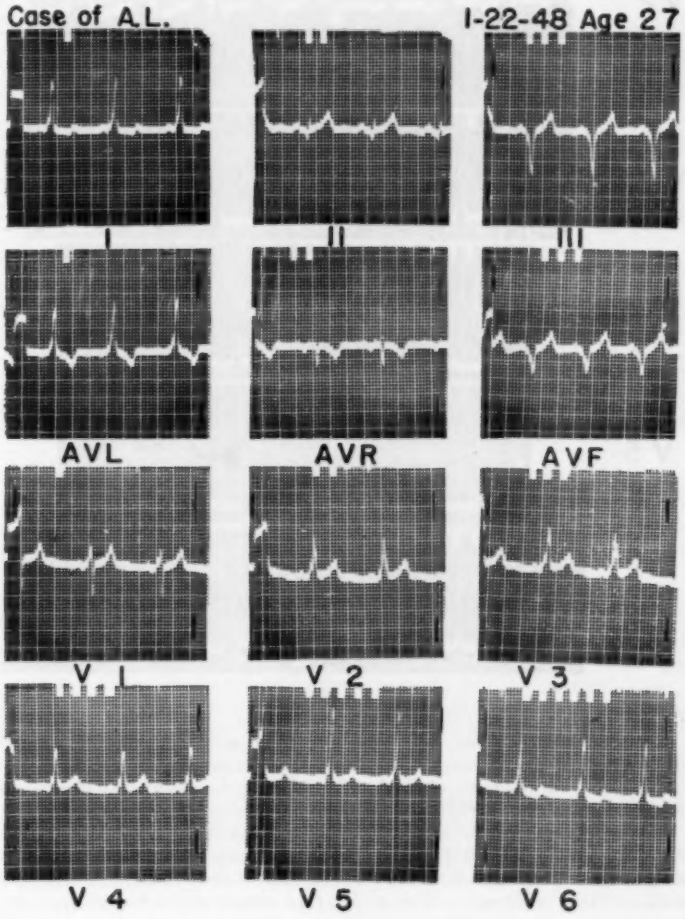


FIG. 1.

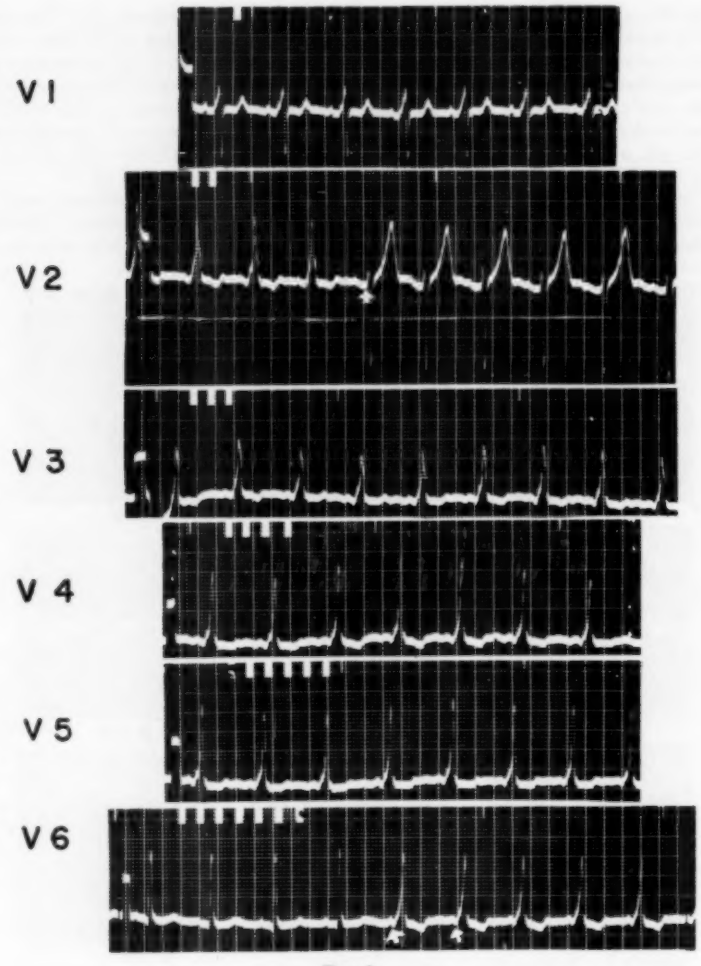


FIG. 2.

dence of cardiac enlargement. The liver and spleen were not palpable. There was "parrot beaking" of the fingernails, but there was no cyanosis.

Serial electrocardiograms showed a Wolff-Parkinson-White syndrome (figure 1). Reversion to a normal rhythm was found on various occasions (figure 2). The blood cholesterol, nonprotein nitrogen, chlorides, calcium, phosphorus, and serum proteins were within normal limits. The arm to tongue circulation time was 13 seconds (calcium gluconate method). The Rumpel-Leede tourniquet test indicated decreased capillary resistance. Sternal puncture smears showed mild hyperplasia of all blood forming elements. The bleeding and prothrombin times were within normal

limits. Repeated blood studies showed persistent elevations of hemoglobin, red and white cell counts, and an increased blood viscosity. The total blood volume was 7,140 c.c. using the Evans blue dye. (The normal total blood volume in the case of this 70 kg. male would be 5,333 c.c.) Studies of the heart, including roentgenograms, fluoroscopy, and diodrast studies of the cardiac chambers, failed to show any abnormalities in configuration.

In the hospital the patient experienced one episode of paroxysmal tachycardia. The pulse rate at this time exceeded 200 beats per minute. The attack began while the patient was at rest, had a sudden onset, and terminated spontaneously in approximately five minutes. Unfortunately the attack subsided before an electrocardiographic tracing could be obtained.

CASE OF A. L.

Date	October 20	22	27	November 3	6	14	17	December 3	9	January 8	9	20	23
RBC (millions)	5.50	5.78	6.08	5.75	6.52	6.23	5.95	5.91	5.97	5.83	4.92	5.15	4.45
HGB (gms)	16.5	18.0	17.5	17.5	20.0	20.0	16.5	17.0	17.5	17.0	15.0	15.0	13.5
WBC (thousands)	11.7	10.8	14.2	10.7	15.8	30.5		13.9	12.1				13.3
Polys. (%)	52.	56.	62.	56.	72.	74.		61.	60.				67.
Eos. (%)	11.	9.	5.	6.	10.	10.		11.	9.				4.
Sed. Rate (mm/hr)		1.0	1.0	1.0	0.2	3.0	0.2	1.0	1.0	1.0		10.0	13.0
Hematocrit		61.	60.	59.	58.	58	59.	59.	55.	57.	50.	49.	45
Platelet (thousands)				290.					200.				
Packed cell Vol.			60				59.						45.
Col. Ind.			0.97						0.9				
Vol. Ind.			1.03										
MCV			95 cu				100 cu		90 cu				
MCH			29 cu				28 cu		30 cu				
MCHC			30 %				27 %		32 %				

	November 19	December 3	January 23
MISC. TESTS	Spec. Grav. Blood 1.060 Viscosity, Blood 7.6 Total vol., Blood 7,140. cc	Art. oxygen content 22.1 ML % Ven. oxygen content 14.9 ML % Difference 7.2 ML % Oxygen capacity 22.9 ML %	Spec. Grav. Blood 1059 Viscosity, Blood 5.1 Total vol., Blood 5,540.cc

* 500 cc OF BLOOD TAKEN FROM PATIENT 18 hrs PRIOR TO THESE TESTS

504-484

FIG. 3.

Repeated venesections of 500 c.c. each were performed as indicated on the dates in figure 3. When the red cell count, hemoglobin concentration, and blood viscosity had returned to normal and the blood volume had dropped to 5,540 c.c., the patient was dismissed. In a recent communication (six weeks posthospitalization) the patient reported that the symptoms described on admission had subsided and that he had returned to work.

DISCUSSION

The failure to demonstrate a cardiac septal defect by angiocardiogram, and the normal values obtained in the arterial and venous blood oxygen studies, ruled out an arteriovenous shunt as being responsible for a compensatory polycythemia. This fact, plus the increased total blood volume, indicated that we were dealing with an instance of polycythemia vera. We believe the Wolff-Parkinson-White syndrome to be a coincidental finding. Since the patient's initial complaints were

probably referable to the polycythemia vera rather than to the cardiac conduction anomaly, and because of the dangers of hemorrhage and thrombosis indicated by the decreased capillary resistance and increased blood viscosity, it was felt advisable to initiate active therapy of the polycythemia.

BIBLIOGRAPHY

1. Gaisböck, F.: Die Polyzythämie, Ergebn d. inn. Med. u. Kinderh. 21: 210, 1922. (Quoted from Wintrobe, M. M.: Clinical hematology, 2nd ed., 1946, Lea & Febiger, Philadelphia, p. 592.)
2. Reznikof, P., Foot, N. C., and Bethea, J. M.: Etiology and pathologic factors in polycythemia vera, Am. J. M. Sc. 189: 753, 1935.
3. Stein, M. H.: A Wolff-Parkinson-White syndrome in a case of congenital heart disease, Am. Heart J. 35: 140 (Jan.) 1948.

MYCOSIS FUNGOIDES WITH "TUMOR d'EMBLÉE": REPORT OF A CASE TREATED WITH NITROGEN MUSTARD*

By THEODORE S. EVANS, M.D., F.A.C.P., ANTHONY P. CIPRIANO, M.D., and ERWIN O. HIRSCH, M.D., *New Haven, Connecticut*

THE case to be presented possesses several unusual features and even tends to discount the idea, still held by many, that mycosis fungoides is a disease that, with little reservation, is largely confined to the skin throughout its course. As is well known and taught, mycosis fungoides is a relatively rare but chronic and usually fatal disease of the skin, running a rather progressive course with infrequent remissions, and characterized by four well known stages, any or all of which the patient may pass through.

The first stage is characterized by generalized pruritus which may persist indefinitely and which may defy diagnosis until the better known and recognized lesions of the skin become manifest.

The second stage manifests itself by varied forms of dermatitides such as eczema, psoriasis, erythema multiforme, etc., expressed as macular, papular, urticarial, and bullous lesions. These varied forms may persist without distinctive clinical features or later assume suggestively diagnostic configuration, such as polymorphism and striking coloration. These eruptions may even be composed of a multiformity of lesions and may pass quickly into the third or infiltrative stage, which has as its striking and diagnostic feature progressive infiltration of the skin. As this stage progresses, extensive patches with varied configuration associated with superficial ulceration become apparent.

The fourth, or last, stage is represented by large tumor-like formations that arise from the areas of infiltration. This stage may lead to chronic inanition, exhaustion, intercurrent infection and, finally, death.

The histopathologic changes described in mycosis fungoides include, briefly, thickening of the prickle-cell layer and micro-abscesses filled with lymphocytes.

* Received for publication April 20, 1948.
From the Ward Medical Service, Grace Hospital, New Haven, Connecticut.

Important and diagnostic changes are seen in the cutis in which there is infiltration composed of many cellular types, i.e., lymphocytes, polymorphonuclear leukocytes, eosinophils, plasma cells, and connective-tissue cells of various types, together with pyknosis and karyorrhexis of the individual cells. There is also a tendency for the endothelial cells to clump, forming pseudo-giant cells.

This is the description given by well-known dermatologic texts of the nature and manifestations of this little understood disease entity. On the other hand, current concepts emphasize minimally the cutaneous involvement but stress more the generalized and systemic nature of mycosis fungoides and its close relationship to the family of lymphoblastomas, especially Hodgkin's disease.[3] Many believe mycosis fungoides to be nothing more than cutaneous manifestations of Hodgkin's disease, or perhaps of lymphosarcoma or other diseases of the lymphatic system. This concept will become apparent in the following case report, as cutaneous involvement was negligible while systemic manifestations were prominent and diffuse, suggesting widespread organ involvement. In many cases, in spite of roentgen, systemic and other studies, it becomes extremely difficult to make a diagnosis as to the type of lymphoblastoma, although the cutaneous pathologic changes may be specific for mycosis fungoides. Notwithstanding the arguments suggesting the relationship between the reticulo-endothelial system and mycosis fungoides, Hodgkin's disease, reticulum-cell sarcoma, etc., according to Montgomery,[4] many cases of lymphoblastoma of the skin, especially mycosis fungoides and, possibly, cutaneous Hodgkin's disease, may start out as a benign inflammatory process and, as a result of chronic irritation, change into a true malignant disease whether of leukemic or lymphosarcomatous type.

Our case would seem to fit well with Symmers' original idea that mycosis fungoides is one of the most confusing conditions to be encountered in the domain of medicine. Many expressions of current thought still relate mycosis fungoides to the realm of granulomata, to lymphadenoma, and to many other skin diseases; however, many more opinions seem to agree that mycosis fungoides as a clinical and pathologic entity does not exist. Some observers feel that mycosis fungoides represents a cutaneous manifestation (if there are cutaneous manifestations) of a systemic disease. These manifestations are sometimes preceded by an array of eruptions of many characters and attended or followed by the appearance of tumors or tumor-like growths which may or may not resemble one another clinically. The histologic appearance of these tumor growths or nodular formations demonstrates more or less three different histologic types:

(a) The cutaneous nodules and associated lymphadenopathy present the histopathologic picture seen in Hodgkin's disease. Frazer reported two such cases.

(b) The cutaneous nodules and associated lymph nodes present the picture histologically of a reticulum-cell sarcoma. Symmers reported two such cases. One of these, a female with multiple ulcerative and nonulcerative nodules of the skin of the scalp, neck, chest, and abdomen, was regarded clinically as mycosis fungoides, but at autopsy generalized lymphadenopathy, splenomegaly, infiltrative tumors of the psoas muscles and ovary microscopically showing reticulum-cell sarcoma were found.

(c) The third group of skin tumors and lymph nodes may present histologic changes typical of lymphosarcoma and, in this type, leukemic transformation may occur. Kaposi reported one such case in which the changes in the skin were

so much like those seen in mycosis fungoides that dermatologists classify it as such. Symmers also reported one such case in a woman who presented herself with a tumor of the neck of three years' duration. The overlying skin of the neck was ulcerated, almost generalized lymphadenopathy was seen, and a palpable spleen was found. The patient had been previously diagnosed as having mycosis fungoides. Autopsy revealed massive generalized lymph node enlargements; histologic examination revealed replacement of the nodes by a diffuse collection of large mononuclear cells, together with a few lymphocytes of the small variety. The spleen and liver were similarly infiltrated by these lymphosarcomatous cells. The case which follows could be classified with this latter group.

Case Report

A 62 year old white female was admitted to the Grace Hospital on November 25, 1947, with the following history: Approximately six months prior to admission, the patient noted progressive swelling over the upper and outer quadrant of the right breast, followed shortly after by a similar but smaller swelling over the same area of the left breast. In addition, chestnut-sized enlargement of the lymph nodes under the angle of both jaws was noticed. As time passed, the patient noted gradually increasing shortness of breath, progressive swelling of both arms and of the hands and legs, orthopnea, low-grade fever, anorexia, and general malaise, but only slight pruritus over the area of the sternum. Five months following the onset of her illness, a physician was seen and immediate hospitalization was advised. Just prior to hospital entry the swelling of the right breast had been incised and bloody fluid was obtained. Further details concerning this incident are not available. Except for a history of 11 pregnancies, with nine children living and well, the past, family and social histories were not relevant.

On admission to the Bridgeport Hospital in October, 1947, physical examination revealed a rounded, egg-sized mass beneath the angle of the left jaw, and a left external strabismus was noted. Both breasts were large and pendulous, and in the region between the axilla and upper pole of both breasts was a large area of induration involving the pectoral fold. This induration was more marked on the right and, in addition, the overlying skin on this side was discolored. The right lung was flat to percussion, with absent breath sounds. The liver edge was palpated at the level of the umbilicus.

Laboratory data revealed a trace of albumin with occasional red blood cells and many white blood cells in the urine. The red blood cell count was 4,040,000, with hemoglobin 10.9 gm.; white blood cells, 6,000, with polynuclears 79 per cent, lymphocytes, 10 per cent; monocytes, 11 per cent. Radiographic studies of the chest on the day following admission showed evidence of massive pleural effusion occupying essentially all of the entire right hemithorax. The mediastinum was slightly shifted to the left. In the parenchyma of the left lung were seen scattered small changes of density which could represent the effect of congestion with superimposed bronchopneumonia, though radiographically this could not be distinguished from metastatic neoplastic involvement.

Course in the Hospital: Treatment consisted of oxygen for dyspnea, morphine, and codeine for sedation and cough, penicillin, sulfadiazine, thiamin chloride, ascorbic acid, and stilbestrol. Five days following admission, 5,000 c.c. of sanguineous fluid were removed from the right chest. A section of the skin from the right breast was excised and the specimen was diagnosed by the pathologist as mycosis fungoides. The slides of this tissue were forwarded to Dr. A. Leibow, at the Yale School of Medicine, and the diagnosis was concurred in.

Following the thoracentesis, repeat roentgen-ray examination of the chest showed almost complete clearing of the previously reported pleural effusion on the right. There were confluent densities throughout the lower two-thirds of the right lung field, and while some of this density was thought due to overlying pleural involvement, actual parenchymal infiltration of an inflammatory or neoplastic origin was seriously considered. The patient was discharged 16 days following admission and transferred to the Grace Hospital for nitrogen mustard (Methyl-bis) therapy.

On admission to Grace Hospital the history was essentially that described above.

Physical examination revealed a 62 year old white female both acutely and chronically ill. She was sitting up in bed and coughing frequently; the sputum was whitish in character. Wheezing was audible at a distance, and the outstanding features were marked enlargement of the right breast, the overlying skin of which was reddish-purple in color, and the less though definitely enlarged and edematous left breast.

In the main, the positive findings were as follows: the skin, edematous throughout, was free from isolated or generalized eruptions or tumors except for the area overlying the right breast. There was generalized enlargement of the lymph nodes, including those of the neck, preparotid, axillary, and inguinal regions. The nodes were firm, discrete, non-tender and fixed, and those in the pre-auricular area were the size of chestnuts. The left eye presented external strabismus, and both fundi disclosed yellowish and whitish exudates of varied sizes and shapes. Both discs were discretely outlined. The anatomy of both ears was negative, though the hearing was grossly impaired (attributed to external auditory canal compression due to overlying enlarged lymph nodes). Both breasts were tremendously enlarged and doughy, but the right breast was extraordinary in appearance. The skin was orange-red in color and had the appearance of diffuse carcinomatous involvement, i.e., carcinoma *en cuirasse*. In addition, there were several nodular and nodulo-ulcerated lesions over the upper and outer pole, with a brawny-hard and indurated feel to the right pectoral fold. Several papular and nodular brick-red eruptions were seen in the skin overlying the sternum. These were pruritic. Also noted was a large, gaping, grossly infected linear wound, measuring 3 cm. by 2 cm., over the mid-portion of the right breast (site of previous biopsy).

Examination of the lungs revealed bilateral impairment of tactile fremitus and percussion note over the lower two-thirds of the right lung and lower one-third of the left lung, with distant to absent breath sounds and many coarse moist râles with superimposed wheezing over the same area. Palpation and percussion suggested slight cardiac enlargement with a soft blowing systolic grade two murmur at the apex. There was definite ascites, with a large, firm though regular liver that extended four fingers'-breadth below the costal margin and a spleen that, by percussion, suggested enlargement to a slight degree. There was a third degree cystocele and rectocele, and the uterus and adnexae were not palpated. The neurologic examination was not remarkable.

Laboratory Data: On admission, the rectal temperature was 102.6° F., pulse 116, respirations 32, blood pressure 140/84 mm. Hg. The red blood count was 3.90, with 75 per cent hemoglobin (Dare). White blood cells: 14,100, with 80 per cent polynuclears, of which 13 per cent were non-segmented; 14 per cent small lymphocytes and 6 per cent large lymphocytes. Platelets 155,000 (normal 150,000 to 250,000 per cu.mm.). Prothrombin time 14 seconds (control 14 seconds). Urine, amber colored; specific gravity 1.015, 1 + albumin, and occasional white blood cell in the sediment. Fasting blood sugar 95 mg. per cent, non-protein nitrogen 33 mg. per cent, icterus index 3.6, total serum proteins 5.34 gm., cephalin-flocculation negative.

On the day of admission, roentgen-ray examination of the abdomen showed extensive hypertrophic osteophyte formation of the dorsal-lumbar spine. The skull

showed no evidences of osteoblastic or osteolytic areas, and the pelvis, though somewhat obscured by gas shadows, could be interpreted as negative. Pertinent findings by roentgen-ray in the chest revealed bilateral effusion with moderate increase in the transverse diameter of the heart. Lymphangitic metastases involving the lung fields could not be excluded. Superimposed pulmonary congestive changes associated with non-specific pneumonitis in both bases were noted.

On the day of admission, attempts at thoracentesis were not successful because of the patient's critical condition, though one later attempt resulted in the aspiration of frankly bloody fluid. A sternal bone marrow specimen was not particularly revealing, other than showing the absence of a leukemic process. A few more than the normal number of eosinophiles, some quite young, were noted.

The patient's course in the hospital was characterized by an almost constant and severely annoying productive cough, associated wth orthopnea. It made sleeping impossible and left the patient utterly exhausted. Other prominent features were anorexia, low-grade fever, progressive weight loss, and general deterioration. Three days following admission, two rather large and firm lymph nodes were removed from the right anterior triangle of the neck, which microscopically revealed complete absence of the normal lymph node architecture with replacement by a very cellular and anaplastic-looking tumor. Nearly all of the cells were of the size of lymphoblasts or larger, with frequent mitotic figures. No Dorothy-Reed cells were seen, and the pathologist's impression was "a highly malignant lymphoblastoma."

On the patient's fifth hospital day, a course of nitrogen mustard (Methyl-bis) was instituted. Because of the unusually poor physical status of the patient it was decided to administer, intravenously, 5 mg. of the drug once daily for four days: total, 20 mg. Just prior to the institution of therapy, the blood count was: red blood cells 3.51; hemoglobin 66 per cent; white blood cells, 8,400, with 89 per cent polynuclears.

Throughout the course of this treatment, neither immediate nor late systemic, hematopoietic or other reactions were noted. Almost daily blood counts averaged white blood cells, 6,500, with 60 per cent polynuclears, until seven days following institution of therapy, when the total white blood cell count began falling, so that on the fourteenth post-treatment day the total white blood cell count was 2,100, with 66 per cent polynuclears.

However, on the eighth day following the beginning of therapy, or on the fifth day following the last injection of nitrogen mustard, a definite change in the clinical picture became evident, that is, the objective signs of improvement far outweighed the subjective ones. There was definite diminution of the generalized state of anasarca, and both breasts had decreased definitely in size. The turgor seemed less and the left breast seemed to have returned to almost normal size. The regressive changes in the right breast appeared less dramatic. However, the size and extent of the generalized lymphadenopathy had been reduced unbelievably. Roentgen-ray examination of the chest at this time revealed areas of clearing in the left lower and right mid-lung fields. These general signs of regression appeared to continue. Other supportive measures consisted of blood transfusions, vitamins, parenteral fluids, and sedation for comfort.

All in all, this period of apparent and spectacular improvement lasted approximately two weeks when, together with increasing severity of the cough, the patient noted severe pruritus and the appearance of numerous coppery-red colored "bumps" over the anterior upper chest below the right clavicle and overlying the sternum. Examination of this area revealed multiple crops of both vesiculo-papular and rosy-red lesions of the skin. These were of varied sizes, but rather concentric in contour. The left breast appeared moderately edematous over its extreme dependent portions; the right breast seemed to remain brawny-hard, with a reddish-purple hue to its color. The lung fields were clearer, though the breath sounds and percussion note suggested

residual involvement of the pleura and parenchyma over the right and left lower lung areas. The right hand and arm remained edematous and the spleen could be felt only with difficulty, though the liver was palpable one to two fingers'-breadth below the costal margin. The generalized lymphadenopathy remained minimal.

On the patient's twenty-fifth hospital day the total blood count was: red blood cells, 3.92; hemoglobin 75 per cent; white blood cells, 4,600, with 70 per cent polynuclears; platelets 110,000 (normal 150,000 to 250,000). Because of the gradually increasing eruption previously noted, associated with other signs and symptoms of continued progression of the disease—i.e., increasing febrile swings, coughing, dyspnea, and edema—a second course of nitrogen mustard (Methyl-bis) was instituted, with the daily dose calculated at 7 mg. for a total of four days: total, 28 mg. No immediate effects were noted from this course of medication.

In spite of additional supportive measures, i.e., oxygen, transfusions, intravenous glucose and vitamins, etc., the patient continued a downward course. Her last few days were spent sitting in bed bent forward in a jack-knife fashion breathing rapidly and with extreme effort. The complexion was pallid and pasty, and the rash over the anterior chest had increased in extent. The right breast had definitely increased in size and appeared stony-hard and brawny. The patient finally died on the twenty-eighth hospital day, the day of her last nitrogen mustard injection.

Autopsy Report: The body was that of a normally developed, obese woman. Rigor mortis was present. Body length 150 cm. There was massive edema of both arms but this was much more marked on the left. There was 4 plus edema of the ankles and legs and 2 plus edema of the thighs and over the sacrum. The breasts were obese and, in addition, made huge by brawny edema, more marked on the right. There was no discharge from or retraction of the nipple. There was a typical peau d'orange appearance to the overlying skin. In the outer lower quadrant of the right breast there was a 3.5 cm. wound (due to biopsy performed before admission). Gross evidence of infection was present. The surrounding skin was purplish in color (apparently due to staining with gentian violet used in the treatment of the wound). The skin overlying both breasts and the anterior chest was covered by flat papules, fairly uniform in size, averaging 3 mm. in diameter and perhaps 1 to 2 mm. high. Over the posterior margin of the right sternocleidomastoid muscle there was a 7.5 cm., well-healed surgical scar. Otherwise the skin was clear.

The lymph nodes in the occipital, pre-auricular and post-auricular, anterior and posterior cervical, axillary and inguinal areas were greatly enlarged, stony hard, and matted. The epitrochlear nodes could not be palpated but may have been obscured by edema. The right pre-auricular group was particularly prominent and measured 10 by 3 cm.

The abdomen was protuberant but no fluid wave could be elicited. A mass was palpable extending from the left costal margin at the midclavicular line to the right flank 10 cm. below the costal margin.

On sectioning the breasts there were many discrete round firm nodules, varying in diameter from a few millimeters to 5 cm. On sectioning they were homogeneous, firm but not gritty. There were no areas of degeneration or cyst formation. These nodules were contiguous but not confluent. They replaced the normal breast tissue to such an extent that only septa-like strands of fatty and fibrous tissue remained between them. No glandular tissue was recognized. These nodules continued in similar arrangement throughout the chest-wall and onto the pleura and pericardium.

When the chest was opened the nodules were seen to penetrate into the right lung. On the left side they did not extend beyond the parietal pleura. A moderate amount of clear straw colored fluid was found in each pleural cavity.

The right lung weighed 1,180 gm. and was firmly adherent to the chest wall and, on section, showed massive infiltration with apparently malignant tissue. Small

nodules similar to those seen in the breasts were found throughout the parenchyma. The left lung weighed 700 gm. and was not adherent, was easily removed and, on sectioning, presented normal architecture except for patches of consolidation in the left lower lobe from which thin pus could be expressed.

The heart weighed 360 gm. There was a normal amount of fluid in the pericardial cavity. The heart muscle appeared small and flabby. There was minimal calcification of the aortic ring. The coronary vessels were not sclerosed. All valves were normal. No scar was found on sectioning the myocardium.

The liver weighed 2,020 gm. It appeared congested but no infiltration with malignant tissue was recognized.

The spleen weighed 240 gm. and contained several large white firm nodules.

The right kidney weighed 150 gm.; in the capsule there were several pin-head sized whitish nodules. The capsule stripped easily and the kidney showed normal architecture. The left kidney weighed 180 gm. and contained four large white nodules in the cortex. The capsule stripped readily and, apart from destruction caused by the nodules, the architecture was normal. The adrenals appeared intact.

The pancreas was normal.

The stomach and duodenum were normal. The gall bladder was thin-walled and without stones.

The omentum and mesentery were studded with whitish and pinkish nodules, varying in size from a pin-head to a grape. The bowel itself showed no abnormalities.

There were also implants on the surface of the uterus and other pelvic organs.

Microscopic Examination: An attempt was made to classify the tumor which has already been described in gross and which was found in many tissues of the body. In general, it may be said that the tumor cells were essentially the size of lymphoblasts, though some larger cells were seen. An occasional adult lymphocyte was identified. Though it seemed reasonably certain that this cell represented a malignant lymphoblastoma, we wished confirmation of this opinion and sections were therefore sent from both the biopsy and autopsy specimens to Dr. Tracy Mallory,* who reported as follows: "I have looked over the slides of your patient with the multiple tumors of the breast, skin and so forth. I agree entirely with your diagnosis of lymphoblastoma. Under the classification that we use here, I would have called it malignant lymphoma, lymphoblastic type. These have the poorest prognosis of the entire group. The median survival period from first symptoms is somewhat less than six months."

No tumor growth was found in the heart, pancreas, liver or adrenals, and only a few scattered cells resembling tumor cells were recognized in them. Otherwise the microscopic examination adds nothing essential to the gross description.

Comment

In attempting to study the literature on the use of nitrogen mustard therapy in mycosis fungoides, it has been evident that most of the cases treated with this form of therapy have been of the diffuse skin type. In general, this type has responded well to nitrogen mustard. This disease was first described by Alibert in 1806 as a syndrome with diffuse lesions of the papillary layer of the skin. Later, two separate types were described: (1) cases which began as diffuse dermatosis (simulating lichen planus), urticaria, eczema and pemphigus, terminating in the form of fungoid lesions, and (2) cases in which tumor developed without preceding premycotic or infiltrating lesions, which were called by Vidal and Brocq in 1885 "mycosis fungoides à tumeurs d'emblée."

Henstell and others reported six cases which they had treated with nitrogen

* See item 7 of bibliography.

mustard. Cases 1, 2, 3, 4, and 5 gave histories from one and one-half to 30 years of skin lesions of various types, with itching as a prominent symptom. They noted moderate enlargement of the lymph nodes in these cases. In Case 6, actual fungoid lesions and ulcers were noted which responded dramatically to treatment, and even in this instance there was a premycotic history of 15 months. In this last case, although the fungoid lesions healed, the patient was considered not to have profited much from the treatment. Our case is distinctly one of the second type, and tumor manifestations were concurrent with the first appearance of skin lesions. Though there was dramatic improvement in the skin lesions and tumors from the nitrogen mustard therapy, this proved to be ephemeral and the patient succumbed to visceral lesions before a second course could be completed. Autopsy revealed widespread visceral lesions which were considered to be due to a very malignant lymphoblastoma. The mycotic fungoid lesions of the skin were only peripheral expressions of generalized lymphoblastosis. Similarity to Henstell's Case 6 is found in the fact that lymphocytes made up a vast majority of the cellular elements seen in the skin biopsy and at autopsy. They called attention to the fact that lymphatic tissue responded less well to nitrogen mustard than did those tumors which show more cells of reticular origin.

In the pooled literature of the National Research Council, 14 cases of mycosis fungoides were reported as treated with nitrogen mustard. Several of these had tumors infiltrating the skin which responded to nitrogen mustard therapy (notably, Cases 439, 129, and 626). However, all of these also had premycotic lesions, and no report of autopsy was found in the history of any of these cases. For that reason we have reported and classified this case as a failure, since life was not notably prolonged by nitrogen mustard therapy. Still, the remarkable subsidence of the fungoid lesions and tumors bears evidence to support the contention that this type is also susceptible to nitrogen mustard therapy. Had it been possible to treat the patient earlier in the course of the disease, it seems reasonable to suppose that much more benefit would have accrued.

Summary

1. A case of mycosis fungoides *à tumeur d'emblée* is reported.

2. The individual lesions of the skin and the peripheral lymph node tumors subsided dramatically under treatment with nitrogen mustard.

3. Autopsy revealed widespread visceral lesions which are classified pathologically as lymphoma of very malignant type.

Our thanks are extended to Dr. C. J. Bartlett and Dr. David Karnofsky for helping us in the study of this case.

BIBLIOGRAPHY

1. Andrews, G. C.: Diseases of the skin, 2nd ed., 1938, W. B. Saunders Company, Philadelphia, page 749.
2. Jacobsen, L. O., Spurr, C. L., Barron, E. S. G., Smith, T., Lushbaugh, C., and Dick, G. F.: Nitrogen mustard therapy, J. A. M. A. **132**: 263–271, 1946.
3. Symmers, D.: Mycosis fungoides as a clinical and pathologic non-existent, Arch. Dermat. and Syph. **25**: 1, 1932.
4. Montgomery, H.: Mycosis fungoides, lymphoblastoma of the skin, and allied conditions as general diseases, Oxford Medicine, Christian and Mackenzie, Vol. 4-336; Section 44: Chapter 1-A, pp. 1–19.

5. Henstell, H. H., Tober, J. N., and Newman, B. A.: The influence of nitrogen mustard on mycosis fungoides, Blood 2: 546, 1947.
6. Nitrogen Mustards: Laboratory and clinical studies from the American Association for the Advancement of Science, Monograph 1947.
7. Personal communication from Dr. T. Mallory, Massachusetts General Hospital.

GENERALIZED PRIMARY LYMPHANGIOMAS OF BONE: REPORT OF CASE ASSOCIATED WITH CONGENITAL LYMPHEDEMA OF FOREARM *

By RAYMOND HARRIS, M.D., *Albany, New York*, and
ANDREW G. PRANDONI, M.D., *Washington, D. C.*

ALTHOUGH lymphangiomas of various bodily structures are described, review of available medical literature reveals only one previously reported account of primary lymphangioma of bone.[1] This present case of widespread, multiple, cavernous bone lymphangiomas associated with congenital lymphedema of the left forearm warrants recording because of its provocative diagnostic and etiologic considerations, as well as its rarity.

CASE REPORT

A white unmarried Army private, aged 20, entered Walter Reed General Hospital on August 12, 1946, complaining of swelling of his left forearm. Present since birth, this condition had increased markedly in 1933, when he was seven, after the injection of diphtheria antitoxin somewhere into his left arm. It was also at about this period that the youth first noted the development of left axillary masses.

At the age of nine the patient had a rib injury after comparatively slight contact while playing soccer. Routine roentgenograms taken on May 1, 1935, after this injury demonstrated "destructive lesions" of the seventh right rib as well as of the fifth and sixth left ribs, with a probable pathologic fracture through the last. There was expansion of the anterior portion of the fifth right rib. The internal aspect of the lower end of the left humerus showed the same type of lesion. Review of the films at that time by several well-qualified radiologists led to the conclusion that the most likely diagnosis was multiple hemangiomas.[2]

When the patient was 15, a biopsy of the left axillary mass revealed a cavernous type of lymphangioma. No evidence of malignancy was found in the sections.[3] Following this operation the youth discovered that his left upper extremity was slowly increasing in size.

In 1943, at the age of 17, the patient developed severe lymphangitis of the left upper extremity which rendered him acutely ill for one week. No etiologic explanation for this condition was found. Between 1944 and 1945 he was exposed to radiation while working as a cyclotron operator, but remained asymptomatic except for slight aching in the affected extremity. Routine physical examinations performed frequently by his employer's medical staff uncovered no deleterious effects of the radiation exposure. Specimens of semen during 1945 were normal.

Shortly after his induction into the Army on May 14, 1946, the youth entered an Army General Hospital where a second left axillary biopsy again revealed a

* Received for publication February 24, 1948.

cavernous lymphangioma. He returned to duty and completed basic training uneventfully, except for one episode of mild lymphangitis of the left upper extremity treated with warm saline applications. He noted after exercise that his affected extremity perspired less than the rest of his body. Subsequently he was rehospitalized and transferred to Walter Reed General Hospital for disposition.

Past history revealed that the youth had had brownish skin discolorations since birth on February 3, 1926. As a child he had had measles and mumps. Later he had developed seasonal hay fever. No evidence of precocious puberty could be elicited. He abstained from fatty foods because they nauseated him. The remainder of the review of systems was negative.

The family history was essentially normal. As far as the patient knew, no other member of the family had a similar condition. His mother, aged 51, was alive and in good health. She was separated from his father, who was also well. One brother, aged 31, had served in the Marine Corps, where routine chest roentgenograms apparently revealed no pathologic lesions.

Correspondence with the patient's mother revealed that she had been suffering from an undiagnosed type of throat condition several months prior to the patient's birth. This condition caused her "to swallow, spit and choke much of the time."

Physical Examination: The patient was a well-developed, slender white male of 20 who weighed 150 pounds. He appeared well-balanced mentally, intelligent and cooperative. His hair distribution was normal. Multiple light brownish pigmented areas of varying sizes and benign appearance were distributed over the surface of the body. The majority of these circumscribed macular spots appeared on the left side of the chest anteriorly and posteriorly. The largest one, measuring 1 cm. in diameter, was located in the second left interspace adjacent to the sternum. The next largest, quite hairy and slightly darker than the rest, was situated on the medial aspect of the right thigh. These pigmented areas followed no definite patterns of distribution.

The teeth were unremarkable. The tonsils had been surgically removed. The thyroid gland felt normal and within it no tumors could be palpated. The remainder of the examination of the head, eyes, ears, nose and throat was normal.

In the left axilla two well-healed surgical scars were visible. No lymphatic nodes were palpable in this region except for a small one in the left supraclavicular fossa. In the right axilla, as well as in the inguinal regions, a few small shotty glands of moderately firm consistency were felt.

The left forearm was perceptibly larger than the right on inspection. Five inches from the olecranon process it measured 11.5 inches in circumference; the right forearm, 10 inches. The doughy swelling of the left upper extremity produced by the readily pitting, edematous-like subcutaneous tissue extended most noticeably between the elbow and wrist. As the contents of the left forearm were milked toward the shoulder, the proximally situated lymphatic vessels and tissues distended gradually. Elevation of the left forearm produced a visible movement of subcutaneous fluid toward the shoulder. Hair distribution on both upper extremities was similar. No gross differences in temperature or color were found. Both extremities were equal in length.

The peripheral blood vessels appeared normal throughout the body except for the dorsalis pedis arteries, whose pulsations were not palpable bilaterally. Neurologic examination disclosed slight reduction of the reflexes in the left upper extremity, presumably caused by the subcutaneous edema.

The subcutaneous tissue of the chest in the vicinity of the left anterior axillary line, resembling the tissue of the left forearm, showed persistent mild pitting edema on pressure. The remainder of the examination was unremarkable. The heart and lungs were normal. The blood pressure in the right arm was 130 mm. Hg systolic, 70 mm. diastolic. Palpation and percussion of the bones produced no pain, and no

changes in the surface contour of the bones could be demonstrated. The liver was not enlarged. The genitalia were those of the average male. The voice was medium pitched and unremarkable.

Hospital Course: When a routine chest roentgenogram disclosed cystic lesions of the ribs, complete skeletal examination was ordered. This demonstrated generalized cystic lesions involving almost every bone. The skull films showed irregular cystic areas, ranging in diameter from 0.5 to 1.5 cm., distributed predominantly in the vault and in the petrous portions of the temporal bones (figure 1). The sella turcica appeared normal.

FIG. 1. Lateral roentgenogram of skull demonstrating multiple cystic lesions.

The bodies of the cervical vertebrae displayed similar cystic changes, without constant definite localization but with considerable roughening of the adjacent areas. The neural foramina in the cervical spine appeared enlarged, and the superior borders of the fourth, fifth and sixth cervical vertebrae showed erosion. The dorsal vertebrae were osteoporotic, but their bodies revealed fewer cystic changes than were noted in the cervical ones. Extensive lesions were found in the bodies and transverse processes of the lumbar vertebrae. The sacrum and coccyx were not shown well by the roentgenograms. Cysts of varying sizes were distributed throughout the pelvis.

Practically all the ribs were involved, although no constant distribution could be detected. At the sites of these lesions the cystic expansions caused widening of the

ribs. The humerus appeared to be involved bilaterally (figure 2). The ulnar bones displayed similar cystic expansions of the proximal ends on both sides. Several areas suggestive of early minimal lesions of the medulla were noted in the middle of the right and left shafts of the femora. In the upper one-third of the left tibia trabeculated cysts were seen. Several small lesions were visible in the right scapula.

No definite lesions were detected in the clavicles, left scapula, mandible, fibulae, radii, or bones of the wrists, hands, ankles and feet. Roentgenograms of the teeth demonstrated only slight alveolar resorption, with impacted R 8 and L 8.

A chest roentgenogram revealed that the heart and great vessels were normal. No pathologic lesions were seen in the lung fields. On the basis of the generalized cystic degeneration, the radiologist suggested that the condition was "polyostotic bone disease due to hyperparathyroidism or polyostotic fibrous dysplasia."

FIG. 2. Note cystic lesions in proximal end of right humerus, as well as in scapula and transverse process of D 6.

While the patient was being studied, a report of additional roentgenograms taken on October 31, 1936, was received. Comparing the films taken then with those taken 18 months earlier (on May 1, 1935), the radiologist stated that the irregular areas of rarefaction in the skull showed the same distribution as on previous examination, without evidence of new areas of involvement. He felt, however, that there had been an increase in some of the bone lesions and that new lesions had developed, namely, in the ribs of the left side and the upper end of the left tibia.[2] Comparison of the 1936 report with the report of the roentgenograms at Walter Reed General Hospital suggested that further bone involvement had occurred since 1936.

Laboratory Studies: Representative laboratory studies were as follows: 5,000,000 erythrocytes per cu. mm.; hemoglobin, 15.3 gm. per 100 c.c.; 9,400 leukocytes per cu. mm.; differential counts: 66 per cent neutrophiles, 31 per cent lymphocytes, 3 per cent eosinophils; urinalysis: normal; no Bence-Jones proteinuria; Kahn reaction, hema-

tocrit readings, clotting and bleeding times, platelet count, bromsulfalein liver function test were all normal. Repeated electrocardiograms were normal. Urinary calcium excretion tests were unsatisfactory.

Blood chemistry determinations showed: urea nitrogen, 13.8 mg. per 100 c.c.; glucose, 95 mg. per 100 c.c.; chlorides, 410 mg. per 100 c.c.; cholesterol, 144 mg. per 100 c.c. serum; carbon dioxide combining power, 52.3 vol. per cent; blood acid phosphatase, normal.

	Sept. 11, 1946	Nov. 22, 1946	Dec. 2, 1946
Calcium (mg. per 100 c.c. serum)	11.5	12.6	
Phosphorus (mg. per 100 c.c. serum)	3.7	3.6	
Alkaline phosphatase (Bodansky units)	2.9	2.9	
Total serum proteins	8.6	6.77	
Serum albumin	6.3	4.79	
Serum globulin	2.3	1.98	
A/G ratio	2.74	2.41	
Fibrinogen (plasma)			0.2

Differential Diagnosis: The most seriously considered disease entities included (1) hyperparathyroidism, (2) polyostotic fibrous dysplasia, and (3) multiple hemangiomas.

With the exception of the multiple bone cysts, there was insufficient evidence pointing to the diagnosis of hyperparathyroidism. No tumor of the parathyroid glands was palpated. Clinically, the patient was asymptomatic as far as bone pain and other symptoms were concerned. Although roentgenograms showed multiple cystic lesions, generalized decalcification of the skeleton so often found in von Recklinghausen's disease was lacking.[4] This, together with the normal blood calcium, phosphorus, alkaline phosphatase, the long asymptomatic history, and the essential good health of the patient, also rendered unlikely the diagnosis of hyperparathyroidism.

Consequently, polyostotic fibrous dysplasia, or Albright's syndrome,[5] was felt to be a more logical diagnosis. This syndrome includes osteitis fibrosa on histologic examination, brown non-elevated pigmented areas of skin which tend to be on the same side as the bone lesions, and an endocrine dysfunction which in the female is associated with precocious puberty. Hence it appeared to fit most of the salient data, elicited in this case, including the normal blood values for calcium and phosphorus. The pigmentation which Albright [6] considered to be a cardinal feature of the disease was, however, not typical in this patient.

The diagnosis of multiple hemangiomas also seemed a good possibility, especially since the patient already displayed one congenital anomaly, and several competent radiologists had already made the diagnosis of hemangiomas of bone.

Lymphangiomas of bone was a more remote possibility, considering its rarity. Paget's disease of bone was unlikely in view of the patient's age, the normal blood chemistry, and the lack of typical roentgenograms. The absence of an enlarged liver or spleen, diabetes insipidus, exophthalmos, and the presence of normal blood cholesterol as well as normal blood picture discredited the diagnosis of Hodgkin's disease, Hand-Schüller-Christian disease, Gaucher's disease or other disturbances of lipid metabolism. Eosinophilic granuloma and Letterer-Siwe's disease, now accepted as phases of the Hand-Schüller-Christian syndrome,[7] were briefly considered.

To arrive at a definite pathologic diagnosis, a rib biopsy was performed on October 8, 1946, under general anesthesia with the preoperative diagnosis of Albright's syndrome. A segment of the sixth left rib, containing several cystic lesions, was selected. At operation the periosteum over the fusiform expanded cystic rib was found firmly adherent to the cortex of the rib and was stripped with some slight difficulty. Pressure on the cystic portion of the rib caused a slight oozing of whitish clear fluid but no blood from the region. The blood supply to the area appeared normal, and no untoward bleeding followed the excision of the rib section. The periosteum was allowed to remain. The patient recovered uneventfully from the operation.

The gross specimen examined by the pathologist consisted of an 11.5 cm. segment of resected rib, the external surface of which presented a fairly regular, fusiform enlargement measuring 7 cm. in length and attaining a maximum diameter of 1.3 cm. The segment was covered by essentially normal cortical bone, except for several irregular, deeply purple cystic areas. Held before a strong light, the central portion

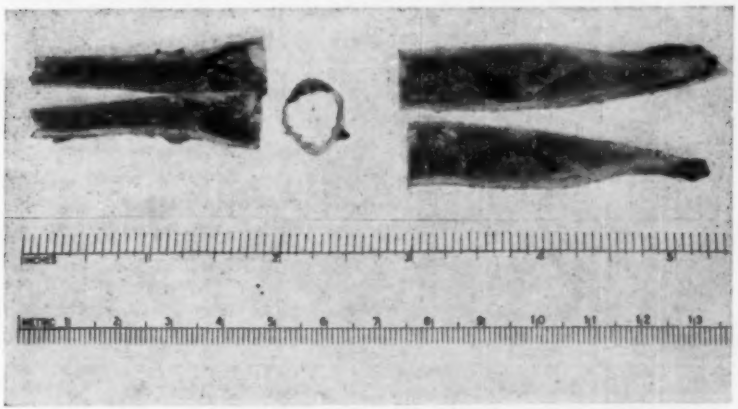


FIG. 3a. Section of left sixth rib divided in half to demonstrate multiple lymphangiomatous cysts.

of the segment appeared translucent. Upon sectioning the specimen, the fusiform portion was found to be composed of multilocular cysts whose linings were irregular and trabeculated but smooth. The walls of the translucent portion were distorted and partially composed of smaller cystic spaces containing watery fluid (figure 3a).

Microscopic examination demonstrated that the normal bone structure of the rib was interrupted by multiple cystic spaces lined with flattened endothelial cells. These multilocular cysts were embedded in the fatty marrow and contained eosin-staining, coagulated material. Collections of lymphocytes and plasma cells were seen at the interstices. The marrow adjacent to the cystic areas varied in appearance from the typical fatty type to one showing active myelopoiesis. The slides made from this specimen were compared with the microscopic sections prepared from the left axillary mass biopsies taken in 1941 and 1946. Marked similarity was noted. The endothelial lining of the spaces in the rib, the coagulated contents, the delicate endothelial network, and the similarity of the cystic lesions in the rib and axillary tissues suggested a lymphangioma of bone (figures 3b, 3c).

FIG. 3b. Low power photomicrograph of rib showing small, multilocular, lymphangiomatous cysts (100×).

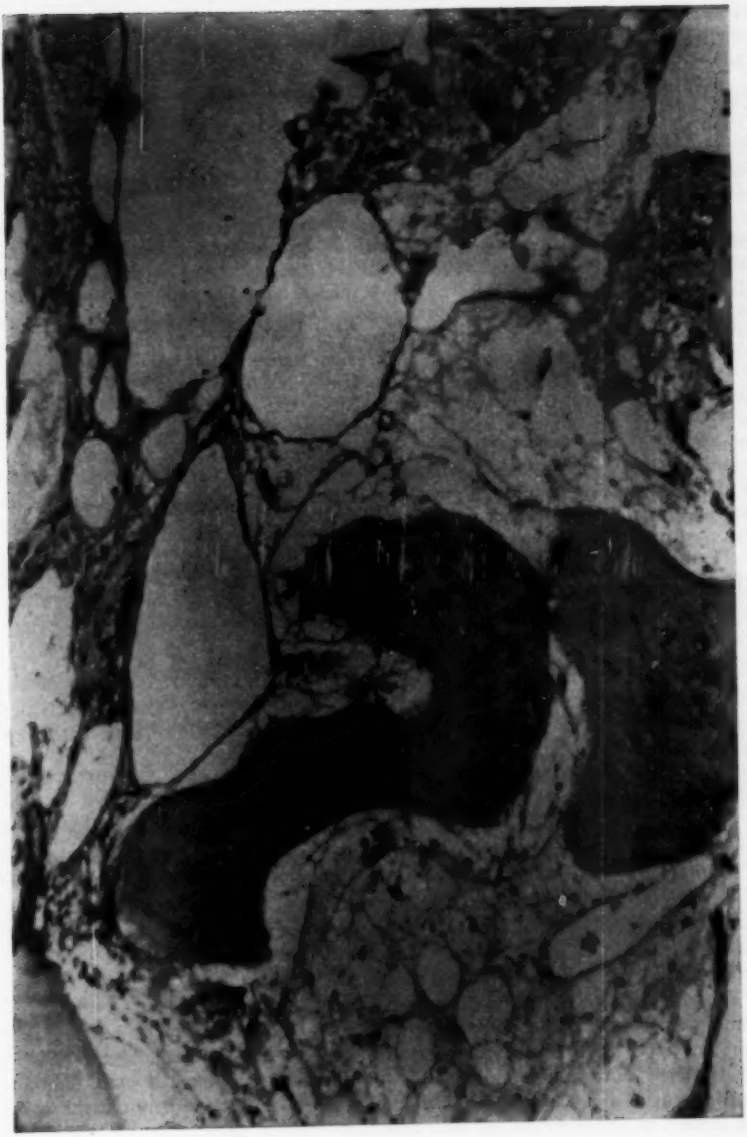


FIG. 3c. High power photomicrograph of rib showing bone trabeculae and lymphangiomatous cysts (440×).

The pathologic diagnosis by Captain Louis Hirsch, pathologist at the Walter Reed General Hospital, was "multiple bone cysts compatible with lymphangioma." These sections were subsequently reviewed by Dr. Charles Geschickter, Professor of Pathology, Georgetown University, Washington, D. C., who confirmed the diagnosis.[8]

The patient continued to feel well in the hospital. Treatment was minimal and mainly symptomatic. It was felt that the diffuse nature of the patient's lesions made it impossible to use effective radiation therapy without seriously incapacitating him. Likewise it was known that, in most instances, cavernous lymphangiomas were resistant to radiation therapy. The patient was therefore discharged from the Army after being provided with an elastic support for his left forearm.

A follow-up examination one and one-half years after initial examination, on January 30, 1948, disclosed that the youth had remained asymptomatic except for slight aching of the left shoulder. In July, 1947, he had experienced slight lymphangitis of the upper left extremity. His weight was now 140 pounds, 10 pounds less than it had been one and one-half years ago. Physical examination was essentially unchanged except as noted below. The areola of the left nipple was observed to be a shade darker than on the right side. The significance of this was not known. In the interim the patient had developed two new subcutaneous masses, presumably lymphangiomas. One, the size of a small marble, was located along the left costal margin near the sternum; the other, slightly smaller, was felt over the lower portion of the sternum. The liver, kidney and spleen were not found to be enlarged.

Laboratory results at this time were as follows: total serum proteins, 6.7 gm. per 100 c.c.; serum albumin, 4.9 gm. per 100 c.c.; serum globulin, 1.8 gm. per 100 c.c.; A/G ratio, 2.72; phosphorus, 4.7 mg. per 100 c.c. serum; calcium, 11.3 mg. per 100 c.c. serum.

Roentgenograms showed no regeneration of the rib at the site of the bone biopsy performed on October 8, 1946, 16 months previously.

Discussion

Primary lymphangiomas of bone are exceedingly rare. A search of the medical literature available at the time the patient was being observed revealed no published cases. Several competent authorities in the field of bone pathology likewise knew of no parallel cases. Subsequently, Bickel and Broders[1] described (April, 1947) what appears to be the first recorded case of primary lymphangioma of bone.

Their patient was a five year old girl with a primary lymphangioma of the ilium. Roentgenograms of her pelvis showed almost complete absence of the left ilium from the sacroiliac joint to the acetabular region. No new bone formation was seen in this area. Films of the skull were normal. Radiation therapy was discontinued when the abnormal tissue did not appear to be radio-sensitive. Marked extension of the destructive process continued, so that more than two-thirds of the left innominate bone disappeared.

The etiology and possible relationships of bone lymphangiomas to other conditions giving comparable osseous lesions merit discussion for the bearing they may have upon the practical considerations of prognosis and treatment. Bickel and Broders[1] note that histologically the periosteum of normal bone contains a rich plexus of lymphatic capillaries and that the tumor in their patient could have arisen in the periosteum and gradually caused dissolution of the ilium, ischium, and portions of the vertebrae by invasion of the blood and lymph spaces contained therein. On the other hand, they felt that the lymphangioma could

also have originated primarily within the bone, since lymphatic vessels do accompany the blood vessels in Haversian canals.

The origin of the bone lesions in the presently described patient is not easily explained. Consideration of the roentgenologic appearance of the lesions and the rib biopsy findings leads one to believe that here the tumors may have originated within the medullary portion of the bone and grown outward to produce expanding lesions in the affected bones. It is more than likely that these multiple tumors are congenital and result from abnormal mesodermal rests which develop into isolated, imperfect lymph vessels with a slight tendency toward abnormal growth.[9] The slowly progressive nature of these lesions in varying stages of development, as indicated by the changing roentgenograms, would seem to indicate that not all of these mesodermal rests became active at the same time and grew at the same rate. The case reported by Bickel and Broders may represent an early stage in the development of this condition, with lesions comparable to those discovered at the age of nine in this patient.

Another plausible etiologic concept is to consider this condition, actually a system disease, as a generalized metaplasia of the reticulo-endothelial system in which some factor as yet unknown caused the cells to produce lymphangiomas. Similarly, generalized hemangiomas in bone and other tissues containing reticulo-endothelial cells might be produced. Thus, lymphangiomas as well as hemangiomas could be related to such diseases of the reticulo-endothelial system as Gaucher's disease, Hand-Schüller-Christian disease and allied disturbances producing similar clinical pictures. In this patient the bone and subcutaneous tissue portions of the reticulo-endothelial system appeared to be involved.

Parsons and Ebb [10] discuss this possibility in their stimulating clinico-pathologic report of a 14 year old girl, showing clinical evidence of the "osseous form of Gaucher's disease," who was found at autopsy to have suffered from cavernous angiomas in the liver, spleen, retroperitoneal glands, thymus, mediastinum, lungs, pleura, kidneys, and most of the bones of the body. They found their case rather difficult to classify, although histologically it was an example of multiple hemangiomas, the cells of which had benign histologic characteristics. In their paper they offer strong support for such a concept relating all these diseases.

With the aforementioned concept in mind, it is interesting to discover that Bucy and Capp [11] describe so-called foam cells in their article on bone hemangiomas. They write that "in several cases cells whose cytoplasm is swollen and largely occupied by vacuoles are seen. These are the so-called foam cells and apparently are merely cells which are undergoing fatty degeneration." They do not say much, however, about the nature of the contents. In one of their cases "many mononuclear eosinophilic and basophilic cells were seen, often alone and often collected in nests. These were apparently myelocytes, the remnants of bone marrow which has been largely replaced by hemangiomatous tissue. Similar cells were seen in the case of hemangioma of the cranium reported by Eros." One cannot help wondering about the relationship of the foam cells and the mononuclear eosinophils described by Bucy and Capp in their cases of bone hemangioma to those found in eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe's disease, all of which are felt to constitute different expressions of the same basic disorder. Certainly further study in this direction is indicated.

The relationship of infection and toxins to lymphangiomas of bone may like-

wise be profitably studied. Bueno [12] observes that certain cells of the reticuloendothelial system are damaged when toxic antigens are introduced into the organism or during infection, and that toxins damage lymphatic tissue. It is noteworthy that the patient in this article developed increased swelling of the left forearm and left axillary masses composed of lymphangiomatous tissue following the injection of diphtheria antitoxin into his left arm. Bickel and Broders in their case state that their patient had had chickenpox just prior to being seen. Since maternal rubella occurring in the early months of pregnancy has been recognized as a cause of cardiac malformations,[13] it is felt that careful family histories of all illnesses, especially during pregnancy, should be taken in these cases of bone lymphangiomas.

The discovery of this condition apparently renders less definite the roentgenologic diagnosis of hemangioma of bone described as a radiologic entity in 1930 by Bucy and Capp.[11] Biopsy in appropriate cases appears necessary to make a definite diagnosis. Of possible value in distinguishing hemangiomas and lymphangiomas of bone may be the diffuseness of lesions in this case, involvement of the cervical, dorsal and lumbar vertebrae being present. Bucy and Capp note, on the other hand, that in hemangiomas of vertebrae the middle dorsal vertebrae are usually involved, and occasionally other dorsal or lumbar vertebrae, but that the cervical vertebrae have always escaped.

The prognosis of this patient appears poor, despite the absence of microscopic evidence of malignant cells. It is believed new lesions will continue to develop. An attempt is being made to follow the course of this patient over a period of years. If his condition becomes more symptomatic, radiation therapy may be tried. If the patient marries and has children, the factor of heredity may be of interest.

Summary

1. A rare case of generalized primary lymphangiomas of bone occurring in a 20 year old white male with congenital lymphedema of the left forearm is reported.
2. The etiology of this condition is discussed.

Note: The authors wish to thank the following for their help in the preparation of this article: Lt. Colonel R. F. Bunch, M. C., radiologist, Walter Reed General Hospital; Dr. Herbert Elias, New York Medical College; Dr. Charles Geschickter, Professor of Pathology, Georgetown University Medical College; Colonel Charles Mueller, M. C., Chief of Medicine, Walter Reed General Hospital; Major J. D. Ashley, M. C., Tilton General Hospital; and Mr. L. Sunny, photographer, Walter Reed General Hospital.

BIBLIOGRAPHY

1. Bickel, W. H., and Broders, A. C.: Primary lymphangioma of the ilium; report of a case, J. Bone and Joint Surg. **29**: 517–522, 1947.
2. Allen, B. M.: Personal communication.
3. Hesmath, F. A.: Personal communication.
4. Snapper, I.: Medical clinics on bone disease, 1943, Interscience Publishers, Inc., New York.
5. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and endocrine dysfunction, with precocious puberty in females, New England J. Med. **216**: 727–746, 1937.
6. Editorial, Polyostotic fibrous dysplasia or Albright's syndrome, J. A. M. A. **135**: 923, 1947.

7. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic granuloma of bone. A condition affecting one, several, or many bones, but apparently limited to the skeleton, and representing the mildest clinical expression of the peculiar inflammatory histiocytosis also underlying Letterer-Siwe disease and Schüller-Christian disease, Arch. Path. **37**: 99, 1944.
8. Geschickter, C.: Personal communication.
9. Allen, E. V., Barker, N. W., and Hines, E. N.: Peripheral vascular diseases, 1946, W. B. Saunders Co., Philadelphia.
10. Parsons, L. G., and Ebb, J. H.: Generalized angiomatosis presenting the clinical characteristics of storage reticulosis with some observations on the reticulo-endothelioses, Arch. Dis. Childhood **15**: 129–157, 1940.
11. Bucy, P. C., and Capp, C. S.: Primary hemangioma of bone, with special reference to roentgenologic diagnosis, Am. J. Roentgenol. **23**: 1–32, 1930.
12. Bueno, P.: Reticuloendothelial cells reacting to toxic antigens and to infection, Arch. Path. **44**: 635, 1947.
13. Gruenwald, P.: Mechanisms of abnormal development, Arch. Path. **44**: 495, 1947.

EDITORIAL

THE PRESENT STATUS OF ELECTROCARDIOGRAPHY

THE indispensable prerequisite to proper treatment is precise diagnosis. Medical diagnosis advances by the accumulation of careful clinical observations and by the utilization of laboratory methods for the detection of disease. The need for more precise diagnosis stimulates the creation and perfection of new diagnostic tools, and these new implements in turn open up new fields of study. Clinical observation is subjective, being dependent upon the keenness of the observer and upon his experience; laboratory methods are ideally objective. In the search for objective evidence to supplement one's clinical impression there is a tendency to overemphasize the value of certain laboratory and mechanical aids to diagnosis. Results of tests expressed in decimal-point percentages or as a graph create the impression of exactness but are no more valuable in helping one arrive at a precise diagnosis than is one's knowledge of the factor which is being measured, its physiological variations, and the limitations of the method of measurement employed. Thus, objective methods must be clearly understood and carefully applied if they are to yield maximum value when blended with clinical observations in the attempt to arrive at a precise diagnosis.

These statements may be applied particularly to the field of cardiology, where the employment of mechanical aids has at times given the physician a false sense of accuracy in diagnosis. So rapid has been the growth and development of electrocardiography that the many discoveries of the electrocardiographer and the electrophysiologist threaten to outdistance the clinician who utilizes this valuable method. It is therefore necessary that one should develop a perspective in this sphere, and such a perspective is enhanced if one views electrocardiography in respect to its origin, development, and its place in clinical medicine.

That an electric current is associated with the activity of the heart has been known for about one hundred years. Kolliker and Muller [1] in 1856 demonstrated that an exposed frog's heart produced an electric current before the commencement of the heart's contraction. Electromotive changes accompanying the action of the human heart were first recorded by Waller in 1887.[2] He employed a capillary electrometer, a device in which the wire from one electrode is attached to a vertical capillary column of mercury, and the wire from the other electrode is connected to the container of sulfuric acid in which the mercury column is supported. A difference in electrical potential between the two electrodes causes the column of mercury to move,

[1] Kolliker, A., and Muller, H.: Demonstration of the negative deflection of the muscle current in physiological contraction of muscle, Verhandl. d. phys. Ges. Wurtzburg **6**: 528, 1856.

[2] Waller, A. D.: A demonstration on man of electromotive changes accompanying the heart's beat, J. Physiol. **8**: 229, 1887.

these movements in turn being recorded on a traveling photographic plate. It is of interest that this pioneer investigator recognized not only the future usefulness of the electrocardiogram but was aware of the limitations inherent in the apparatus used and in the leads employed. He pointed out the small amplitude of the movements recorded, for the inertia of the mercury column obscured fine rapid changes. He noted that differences in the position of the electrodes gave rise to differences in the curves obtained.

Waller strapped one electrode to the front of the chest, the other to the back. He also employed leads from the two hands and from one hand and one foot. Succeeding investigators have made and are making changes in the recording devices and in the sites and combinations of sites from which the current is led off from the body to the electrocardiograph. However, it would be appropriate to recall Waller's concluding statement:

"It is on account of these sources of doubt that I have not thought it advisable at this stage to attempt a definite interpretation of the character of the variation, which although as shown . . . is certainly physiological, may nevertheless be physically complicated by the conditions of demonstration on the human body."

A great advance was the introduction into electrocardiography of the string galvanometer by Einthoven in 1903.[3] This consisted of a fine metal-coated quartz string suspended in a magnetic field. The string moves when an electric current is conducted through it. These movements, optically magnified, are in turn photographed on a moving photographic plate or film. As Einthoven pointed out, the string galvanometer was a more sensitive instrument whose sensitivity could easily be regulated, the curves obtained were directly proportional to the current being measured, and the machine itself was easily operated.

Recent developments in electrocardiographs have taken several directions. The string galvanometer-photographic machine with optical magnification is still popular, in some instances being combined with a rapid film-developing device. Vacuum tube amplification of the electric current produced by the heart has permitted the use of devices with greater inertia such as the Duddell oscillograph,[4] the mirror galvanometer, and the heated stylus. The latter, moving lightly over specially treated paper, produces a record that is instantly visible, eliminating the need for a photographic process. Vacuum tube amplifiers and direct-writing devices possess certain theoretical disadvantages, but for practical purposes they produce acceptable electrocardiograms.[5] The cathode-ray oscillograph is also being used with advantage in electrocardiography. Such a unit has minimal inertia and a maximum degree of frequency response.

[3] Einthoven, W.: The galvanometric registration of the human electrocardiogram, likewise a review of the use of the capillary-electrometer in physiology, Pflüger's Arch. f. d. ges. Physiol. 99: 472, 1903.

[4] Cf. Johnston, F. D., *in* Medical Physics (ed. Otto Glasser), 1944, Vol. I, Year Book Publishers, Chicago, p. 352–361.

[5] Schwarzschild, M., and Kissin, M.: Effects of condensors in the electrocardiograph, Am. Heart J. 9: 517, 1934.

There have been many changes in the type and number of electrocardiographic leads employed. Any combination of sites from which the electromotive force accompanying cardiac activity may be led off from the body is known as a lead. Direct electrocardiograms are recorded when an electrode is placed directly upon the heart and were an early experimental method in laboratory animals. Waller used electrodes placed upon the front and back of the chest, as well as various combinations of electrodes on the extremities. Earlier clinical studies at first utilized "extremity leads."

Any lead records the differences in electrical potential between the two electrodes selected. Where both electrodes have a significant potential the lead is "bipolar." These earlier leads were therefore bipolar. Wolferth and Wood [6] in 1932 described leads in which one electrode was placed upon the precordium, the other on one of the extremities. The precordial (exploring) electrode, being close to the heart, possesses greater potential than the extremity (remote) electrode. The resulting curve is a bipolar lead since the remote electrode still possesses significant potential, and the pattern represents the difference in the potential forces of the two electrodes. These precordial leads were responsible for great advances in the diagnosis of anterior myocardial infarction. At first, one precordial lead was used, the exploring electrode being placed medial to the cardiac apex (Lead IV). Its polarity was later reversed so that it would normally be recorded with the major positive ventricular deflections registered upright, similar to the deflection in the limb leads.

It was soon demonstrated that by the use of multiple precordial leads one could discover small areas of infarction on the anterior wall. Multiple precordial leads were shown by Wilson [7] and his co-workers to provide much more information than a single such lead. Their experimental production of myocardial infarction, studied with intra-cavity and surface records, furnished an excellent basis for later clinical correlation. The transition of R and T waves across the precordium may be disturbed, and a break in this transition may indicate a localized area of myocardial infarction, surrounded by non-infarcted myocardium as shown by the recording of normal precordial electrocardiograms on either side.[8]

Esophageal leads have enabled the electrocardiographer to study posterior parts of the heart. They have proved valuable in the study of auricular activity and the analysis of complex arrhythmias.[9] Esophageal leads have been reported as being of value in the diagnosis of localized

[6] Wolferth, C. C., and Wood, F. C.: The electrocardiographic diagnosis of coronary occlusion by the use of chest leads, Am. J. M. Sc. **183**: 30, 1932.

[7] Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The form of the electrocardiogram in experimental myocardial infarction: The later effects produced by ligation of the anterior descending branch of the left coronary artery, Am. Heart J. **10**: 903, 1935.

[8] Wilson, F. N., Rosenbaum, F. F. and Johnston, F. D.: Interpretation of the ventricular complex of the electrocardiogram, 1947, Vol. 2, Advances in Internal Medicine, Interscience Publishers, N. Y.

[9] Brown, W. H.: A study of the esophageal lead in clinical electrocardiography, Am. Heart J. **12**: 1, 1936.

posterior myocardial infarction by some investigators,[10] while other workers question the validity of such interpretations.[11] More recently, electrodes have been introduced into the human heart itself by the process of cardiac catheterization.[12] These intracavity leads have yielded much information about the form of auricular and ventricular patterns and of variations in cavity potentials.

In 1934, Wilson and his co-workers [13] connected the extremities (RA, LA, LL) through resistances of 5,000 ohms each, to a common electrode, thereby reducing the potential of this remote electrode to almost zero. When paired with an exploring electrode this results in a practically "unipolar" lead, reflecting the potential of the exploring electrode alone. Unipolar leads are used for the study of both precordial and extremity potentials. The unipolar extremity potential may be augmented by a method suggested by Goldberger,[14] in which he removed the 5,000 ohm resistances and the connection of the indifferent electrode to the extremity whose potential is to be determined.

The unipolar extremity leads have been employed particularly in the determination of the electrical position of the heart and in the diagnosis of myocardial infarcts in certain positions. Thus, infarction of that part of the heart facing the diaphragm causes changes in the left leg unipolar lead. Goldberger [15a] and Myers [10b] claim that a normal Q_3 can be differentiated from an abnormal Q_3 in that there is a significant Q wave in aVF associated with the latter. Lowen and Pardee [15b] have questioned the superiority of Q–aVF over Q_3 and Q_2. However, inasmuch as Lead III is bipolar and represents the difference in potential between the left leg and left arm, an upright R wave in the left arm can be represented as a negative value in Lead III. As a result, the registration of an abnormal Q wave in lead aVF is undoubtedly of more value in the diagnosis of an infarct on the diaphragmatic surface of the heart. At times infarction of the upper antero-lateral surface of the heart may be suggested by an abnormal left arm unipolar lead,

[10] (a) Hamilton, J. G. M., and Nyboer, J.: The ventricular deflection in myocardial infarction: An electrocardiographic study using esophageal and precordial leads, Am. Heart J. **15**: 414, 1938. (b) Myers, G. B., and Oren, B. G.: The use of the augmented unipolar left leg lead in the differentiation of the normal from abnormal Q wave in standard Lead III, Am. Heart J. **29**: 708, 1945.

[11] (a) Burchell, H. B.: An evaluation of esophageal electrocardiograms in the prognosis of healed posterior myocardial infarction, Am. J. M. Sc. **216**: 492, 1948. (b) Sandberg, A. A., Scherlis, L., Grishman, A., Master, A. M., and Wener, J.: The Q wave in esophageal electrocardiography, Am. Heart J. **40**: 47, 1950.

[12] Hecht, H. H.: Potential variations of the right auricular and ventricular cavities in man, Am. Heart J. **32**: 39, 1946.

[13] Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms that represent the potential variations of a single electrode, Am. Heart J. **9**: 447, 1934.

[14] Goldberger, E.: A simple indifferent electrocardiographic electrode of zero potential and a technique of obtaining augmented unipolar extremity leads, Am. Heart J. **23**: 483, 1942.

[15] (a) Goldberger, E.: The differentiation of normal from abnormal Q waves, Am. Heart J. **30**: 341, 1945. (b) Lowen, H. J., and Pardee, H. E. B.: Unipolar extremity leads in records with large Q_3, Ann. Int. Med. **31**: 456, 1949.

in the presence of an apparently normal group of precordial leads taken at the usual level. Under such circumstances it has been suggested that further information may be obtained by exploring the precordium at a higher level than usual.[8]

There is therefore available to the modern electrocardiographer a multiplicity of leads from which to choose. A committee of the British Cardiac Society has recommended [16] that bipolar chest leads be discontinued and has stated that "the full electrical exploration of the heart involves the taking of at least twelve leads and sometimes more. The 12 basic leads are: (1) the three standard limb leads; (2) the three unipolar limb leads; (3) the six unipolar precordial V leads. . . . It is possible to limit the leads recorded to a selected few when a particular lesion is suspected."

Electrocardiographic theory has developed and progressed with the changing methods. One must not lose sight of the fact that a unipolar lead records not only the electromotive forces produced by the heart muscle beneath the exploring electrode, but the summation of the electromotive forces of the entire heart as it presents itself at that site.[17] The conventional leads may be pictured as but different projections of one subject: the total electromotive forces of the heart. Taking a multiplicity of leads at various positions aids in trying to compose a single picture of this entity. There have, however, been attempts to secure a picture of the entity itself. Vectorcardiography is such an attempt.

It was early recognized that the electrical forces of the heart may at any one instant be represented by a vector having magnitude, direction, and sense. The vector loop represents the terminus of innumerable instantaneous vectors as it advances during the cardiac cycle. Mann [18] and Wilson et al.[19] initially described the vectorcardiograms as registered in the frontal plane alone. Later attempts to employ "spatial" vectorcardiography have involved the utilization of various methods of spatial representation, including the use of solid models,[17a, 20] stereoscopic projection,[21] and the registration of the projection of the vector loop onto each of three planes.[17a] Although the ultimate choice of spatial distribution of electrodes on the thorax [17a, 22] and the selection of the appropriate recording device and representation remain unsettled, it is undoubted that spatial vectorcardiography

[16] Report of the Committee of the British Cardiac Society: Multiple unipolar leads, Brit. Heart J. 11: 103, 1949.

[17] (a) Duchosal, P. W., and Sulzer, R.: La vectorcardiographie, 1949, S. Karger, Basel, Switzerland. (b) Bayley, R. H.: On certain applications of modern electrocardiographic theory to the interpretation of electrocardiograms which indicate myocardial disease, Am. Heart J. 26: 769, 1943.

[18] (a) Mann, H.: The monocardiograph, Am. Heart J. 15: 681, 1938. (b) Mann, H.: A method of analyzing the electrocardiogram, Arch. Int. Med. 25: 283, 1920.

[19] Wilson, F. N., and Johnston, F. D.: The vectorcardiogram, Am. Heart J. 16: 14, 1938.

[20] Pantridge, J. F., Abildskov, J. A., Burch, G. E., and Cronvich, J. A.: A study of the spatial vectorcardiogram in left bundle branch block, Circulation 1: 893, 1950.

[21] Vastesaeger, M. M.: Les troubles de la conduction intraventriculaire chez l'homme, Acta Cardiol. Supplement 1: 1, 1946.

[22] Wilson, F. N., Johnston, F. D., and Kossmann, C. E.: The substitution of a tetrahedron for the Einthoven Triangle, Am. Heart J. 33: 594, 1947.

will be of additional benefit in the further analysis of complex electrocardiograms, conduction defects, and infarctions.

The ultimate goal of electrocardiography and of the improvement in machines and methods is a more precise electrical study of the heart. It is an invaluable method for the diagnosis of the various disturbances of heart rhythm, especially if supplemented, when necessary, by special technics such as esophageal leads for the demonstration of auricular activity. Electrocardiography has proved very useful in the detection of various types of cardiac disease, especially myocardial infarction. Herrick's description [23] of the clinical picture of coronary artery occlusion (1912) stimulated study of the electrocardiographic changes in this condition. Pardee [24] stressed

FIG. 1. Vectorcardiograms of a normal adult, recorded in the horizontal, frontal, and sagittal planes according to the cube method of electrode placement. (R: right; L: left; P: posterior; A: anterior.) The large loop represents the QRS sE loop: the smaller loop, the T sE loop. The arrow indicates the direction in which the QRS loop is inscribed. Time is indicated by interruption of the QRS loop every 1/400 second. In the horizontal plane, lines V_1 and V_6 indicate the approximate positions of the axes of the V_1 and V_6 electrodes, respectively. The contour of leads V_1 and V_6 may be approximated by the *projection* of the QRS loop upon the respective axes as the loop is inscribed. Inscription of the vector loop toward the electrode results in an upward deflection; movement away from the electrode represents a downward deflection. The deflection is above the baseline on the + side of the intersection of the axes, and is below the baseline on the − side. (Illustration courtesy of Grishman, A., Scherlis, L., Lasser, R. P., Boron, E. R., and Sandberg, A. A.).

the importance of the Q waves in the extremity leads in the electrocardiographic diagnosis of myocardial infarction. With the development of precordial leads, advances were made in the localization of anterior myocardial damage. Wilson's [7] excellent studies in experimental occlusion in animals have helped advance our knowledge of precordial leads in myocardial infarction.

Our clinical application of the electrocardiogram has been largely empirical, based upon the accumulation of, and painstaking analysis of, electro-

[23] Herrick, J. B.: Clinical features of sudden obstruction of the coronary arteries, J. A. M. A. 59: 2015, 1912.

[24] Pardee, H. E. B.: An electrocardiographic sign of coronary artery obstruction, Arch. Int. Med. 26: 244, 1920.

cardiograms, and the correlation of various electrocardiographic patterns with clinical pictures and with autopsy findings. Myers and his co-workers [25] have recently published such a series of electrocardiographic and pathological correlations which are invaluable in the clinical evaluation of electrocardiographic findings.

Interpretation of the electrocardiogram may be based not upon pattern analysis alone but upon the net areas of the QRS and T deflections, or ventricular gradient.[26, 27] Such a determination was originally based upon analysis confined to the frontal plane, but spatial analysis when more accurate may permit a more reliable and quantitative analysis. The ultimate clinical value of the determination of ventricular gradients remains to be shown.

Not only may damage to the myocardium be shown by the registration of Q waves over areas of infarction, but alterations in the RS–T segment may be recorded. The RS–T segment is elevated in leads within the left ventricle when the subendocardium is damaged, and depressed in such instances in epicardial leads recorded directly over the damaged areas. In injury to the epicardial surface, the RS–T segment is elevated in epicardial leads recorded over the damaged areas and depressed in leads recorded within the damaged ventricle.[28] Such reciprocal changes are of importance in localization of electrocardiographic alterations in pericarditis, coronary insufficiency, and subendocardial myocardial infarction.

The increased use of electrocardiography and growing experience with this laboratory method have resulted in an ever-widening range of "normal records" and a lengthening list of the conditions in which the electrocardiogram may be abnormal. It is recognized that patients with apparently normal hearts may have electrocardiograms with certain deviations from the presently accepted range of normal electrocardiographic standards and

[25] Myers, G. B., Klein, H. A., Howard, A., Hiratzka, T., and Stofer, B. E. (in various combinations): Correlation of electrocardiographic and pathologic findings in . . . infarction (of various types), Am. Heart J. I—anteroseptal **36**: 535, 1948; II—anterolateral **36**: 838, 1948; III—anteroposterior **37**: 205, 1949; IV—interventricular septum and right ventricle **37**: 720, 1949; V—posterior **38**: 547, 1949; VI—posterolateral **38**: 387, 1949; VII—lateral **37**: 374, 1949.

[26] Wilson, F. N., Macleod, A. G., Barker, P. S., and Johnston, F. D.: The determination and the significance of the areas of the ventricular deflections of the electrocardiogram, Am. Heart J. **10**: 46, 1934.

[27] Ashman, R., Byer, E., Gardberg, M., Ferguson, F. P., Gremillion, L. I., and Bayley, R. H. (in various combinations): The normal human ventricular gradient, Am. Heart J. **25**: 16, 36, 1943; **26**: 473, 495, 697, 1943.

[28] (a) Schutz, E.: Der monophasische Aktionsstrom, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. **12**: 15, 1939. (b) Wolferth, C. C., Bellet, S., Livezey, M. M., and Murphy, F. D.: Negative displacement of the RS–T segment in the electrocardiogram and its relationships to positive displacement; an experimental study, Am. Heart J. **29**: 220, 1945. (c) Pruitt, R. D., and Valencia, F.: The immediate electrocardiographic effects of circumscribed myocardial injuries; an experimental study, Am. Heart J. **35**: 161, 1948. (d) Hellerstein, B. K., and Katz, L. N.: The electrical effects of injury at various myocardial locations, Am. Heart J. **36**: 184, 1948. (e) Boyd, L. J., and Scherf, D.: The electrocardiogram after mechanical injury of the inner surface of the heart, Bull. New York M. Coll., Flower and Fifth Ave. Hospitals **3**: 1, 1940.

still not necessarily have cardiac disease.[29] We now recognize variations in the electrocardiogram which reflect the position of the heart in the body rather than abnormalities in the heart itself.[8] This is particularly true of a Q_3 and of an inverted T_3. The long list of diseases in which the electrocardiogram may be abnormal now includes the common conditions in which the myocardium is "electrically inert," [17b] such as myocardial infarction; or diffusely involved, such as rheumatic and diphtheritic myocarditis; or hypertrophied, such as hypertension, syphilitic and rheumatic valvular disease, and congenital heart disease. It includes also many infectious diseases, metabolic and electrolytic disorders, nephritis and anemia, among others. Electrocardiograms may be abnormal following exercise or trauma to the heart, in the presence of fever, or as a result of various drugs. Electrocardiographic abnormalities may be caused by hyperventilation or following tachycardia, and they have been reported in patients with neurocirculatory asthenia. These abnormalities include conduction defects and changes in the form and appearance of the various waves.[29]

Conversely, there are conditions in which the heart is damaged but the electrocardiogram is normal.[30] The area of myocardium involved must be sufficiently large and so located that it affects the electromotive force recorded. Because of this, a small area of infarcted myocardium on the anterior wall of the heart is easily accessible to an exploring electrode and therefore more easily detected than a similar area on the posterior wall. A small intramural infarct may produce no electrocardiographic abnormalities. Surface injury predominates over deep cardiac injury in producing changes in the electrocardiogram. Electrocardiographic changes may be delayed in appearance, often not being evident until several days after injury to the heart has occurred. Because there is a range of normal findings rather than a rigid single standard, it is necessary to take serial records. Such a series of records, each of which in itself is "normal," may indicate a significant trend in the direction of abnormality.

As a result of the growing experience in electrocardiography there has developed an awareness not only of the value of this tool, but of the limitations of the method. An electrocardiogram is a record of *one* of the manifestations of cardiac activity—the production of an electromotive force. These tracings, therefore, represent not a picture of the heart muscle, but of its electrical activity. It does not give a picture of the coronary arteries except insofar as a disturbance in the coronary circulation affects the production of an electromotive force by the heart muscle. The electrocardiogram, therefore, does not indicate "coronary sclerosis" or "coronary occlusion" directly, although it may disclose an area of myocardial damage so

[29] (a) Sensenbach, W.: Some common conditions, not due to primary heart disease, that may be associated with changes in the electrocardiogram, Ann. Int. Med. **25**: 632, 1946. (b) Thomas, C. B.: The significance of electrocardiographic abnormalities in young adults, Bull. Johns Hopkins Hosp. **74**: 229, 1944.

[30] Master, A. M.: The two-step exercise electrocardiogram: A test for coronary insufficiency, Ann. Int. Med. **32**: 842, 1950.

situated that the probable cause is interference with the blood flow through a certain coronary vessel.

In the search for electrocardiographic tests to determine the adequacy of the coronary circulation, there have been developed certain stress tests in which the patient is subjected either to standard exercise [20] or to an oxygen-poor atmosphere.[21] Under such circumstances temporary electrocardiographic abnormalities may be observed, from which it may be inferred that the coronary circulation is inadequate or "insufficient." Such tests are frequently useful, but they are not infallible. A negative or normal response may add but little in evaluating an equivocal clinical picture. A positive test is much more reliable, although false positive tests have been reported. Such tests are best applied by those familiar with them because under certain circumstances their application may be dangerous, and the results misinterpreted.

It has been the practice to interpret certain abnormal electrocardiograms as "indicating myocardial damage." When the pattern is such that it can be localized to a specific area, such a statement may be valid. However, since "myocardial damage" carries the connotation of anatomical changes, this term might best be avoided when the electrocardiographic changes are minor and nonspecific. Because of the wide range of normal, a record should be labeled as "borderline" if its proper classification is in doubt. It should be stressed that a minor or nonspecific abnormality in an electrocardiogram as an isolated finding is not sufficient reason to label a patient as having cardiac disease. Many problems remain to be solved, not only as regards the interpretation of the electrocardiogram but also in respect to the electrophysical changes responsible for its production.

It is evident from the preceding discussion that electrocardiography is a potent tool in cardiac diagnosis. Familiarity with the method, its growth and its development, impresses one with its usefulness and with its limitations. The novice in electrocardiography all too frequently lacks perspective and is too much aware of the usefulness and too little aware of the limitations. The stage has not been reached where this tool can supplant rather than supplement clinical judgment. This laboratory method should be but one of the factors which help the clinician arrive at a precise diagnosis and thus enable him to embark upon the proper course of treatment.

S. S.

[21] Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The "anoxemia test" in the diagnosis of coronary insufficiency, Am. Heart J. 21: 634, 1941.

REVIEWS

The Mask of Sanity—An Attempt to Clarify Some Issues About the So-called Psychopathic Personality. 2nd Ed. By HERVEY CLECKLEY, M.D. 569 pages; 22.5 × 14.5 cm. C. V. Mosby Company, St. Louis. 1950. Price, $6.50.

The first edition of this book, published in 1941, called attention to the problem of psychopaths which had plagued families, physicians, psychiatrists, jurists and law enforcement officers for decades. With a timeliness which was almost prophetic, it antedated the profusion of diagnoses of constitutional psychopathic inferiority (C.P.I.) and constitutional psychopathic state (C.P.S.) which were to be made in the war years which followed. Medical and line officers were soon to witness firsthand the havoc these "forgotten men of psychiatry" could create and to experience the impotence of civil and military society in the satisfactory handling of them.

In attempting to revise the first edition, based primarily upon experience with adult male psychopaths, the author found it impossible to do justice to the subject by additions, deletions and corrections, so the book was rewritten and enlarged. The author had learned much and changed some of his concepts in the intervening decade. Spurred by the belief that few medical or social problems so richly demanded a hearing, the author continued his studies drawing his subject material from persons in all walks of life, including the professional man and the scientist. The psychopath, Dr. Cleckley notes, is much more than an ordinarily dissipated and profligate person, though both are noted for being injudicious. An important mask of distinction is that the profligate seeks what everyone can at least interpret as a form of pleasure or surcease from pain, whereas the psychopath's actions rarely resemble the pursuit of pleasure or even necessary analgesia.

Under our present laws these individuals wander about like lost souls from fiasco to fiasco with all gradations of seriousness. The courts, recognizing the apparent irrationality of their acts and the uselessness of punishing them, consign them to mental institutions only to have them discharged quickly, being found "without psychosis." Thus classed as "sane" and ipso facto responsible for their acts in the eyes of the law, they are removed from any possibility of exposure to treatment, feeble as present-day treatment may be. Free to return to their accustomed mode of life, they are soon in trouble again and the whole disheartening process is repeated.

The book consists of five sections divided into 68 chapters with an added appendix. It is well and easily written, sometimes prolix; it is always interesting, enlivened at times by the author's light touch which is always in good taste. Though he disavows all pretense of knowing the answer to the enigma he discusses, he nevertheless presents various suggestions which might bring psychiatrists, courts and communities to closer and more satisfactory grips with the problem. The book is thus highly recommended as a careful exposition of a serious and widespread problem.

F. A. BRACELAND, M.D.

The Practice of Medicine. 5th Ed. By JONATHAN C. MEAKINS, C.B.E., M.D., LL.D., D.Sc., formerly Professor of Medicine, McGill University. 1558 pages; 18 × 26.5 cm.; 518 illustrations. The C. V. Mosby Company, St. Louis. 1950. Price, $13.50.

The first impression of this book is favorable, for its cover and format are attractive. The second impression, however, is less so; for as soon as it is taken in hand it is found to be unconscionably heavy. It is, in fact, a lusty newborn weigh-

ing no less than eight pounds. Thus it exceeds its predecessor of 1944 by one and a half pounds and 114 pages.

The additional pages are mainly devoted to a new section on Chemotherapy and Antibiotics, and an enlarged chapter on Psychosomatic Medicine in place of the previous rather tenuous section on Psychiatry. Whatever one's views on the subject, this chapter is a lucid, well-balanced and helpful statement of the present position of psychosomatic medicine.

The new section on Chemotherapy and Antibiotics leaves much to be desired. First, it is not up to date for a 1950 text. Thus the table on page 1434, purporting to list the drugs of choice in various infections, is antiquated, as it takes no account of chloromycetin or aureomycin. The whole chapter is more or less confined to the sulfonamides, penicillin and streptomycin, with scant recognition of aureomycin and two mere comments about chloromycetin. Then the reader is left in doubt concerning the practicability of oral streptomycin administration for systemic affections; in one place it is stated "it can be readily and effectively given by mouth, by which method a satisfactory blood level can be maintained." A page or two later it is asserted that "there is little or no transfer of streptomycin through the bowel in either direction." Such glaring contradictions make one mistrustful. There are also numerous misprints in this chapter. Altogether one gains the impression that this section was written rather hastily, without adequate revision and editing, about two years ago.

The author states in the introduction that many "seeming sins of omission" are deliberate, because the validity of certain advances has not been sufficiently proved to warrant inclusion in his text. While this is an admirably conservative attitude, it does not seem to justify the antique flavor of the present chapter, nor to excuse a number of undesirable omissions and commissions throughout the text. To draw attention to only a few, should a 1950 text state that there is no specific remedy for typhus? Or base the diagnosis of bundle branch block not only on standard lead tracings alone, but even employ the old nomenclature? Or give no specific treatment for typhoid? Or fail to mention hypersplenism? Again, no consideration is given to the handling of the large and important group of mild diabetics who can be controlled without insulin.

The excellent section on Diseases of the Nervous System by the late Dr. Petersen has been retained, and the chapter on endocrinology has been largely rewritten and expanded.

The text too often lacks the simplicity of style which favors immediate understanding. This is not to say that the text as a whole is not fundamentally sound. The book is unusually well illustrated, and has enjoyed deserved popularity as a standard text in all its editions since the first in 1936. It is not, however, the textbook of medicine that the present reviewer would single out as his choice from among the available selection of texts. In general it is too sketchy for the internist, while its other shortcomings make it inferior to some other obtainable textbooks for students and general practitioners.

H. J. L. M.

Blood Clotting and Allied Problems: Transactions of the Second Conference, January 24–25, 1949, New York, N. Y. Edited by Joseph E. Flynn. 231 pages; 23 × 15 cm. Josiah Macy, Jr. Foundation, New York. 1949. Price, $2.25.

The second conference on blood clotting and allied problems sponsored by the Josiah Macy, Jr. Foundation met in New York City, January 24–25, 1949 under the Chairmanship of Dr. Irving S. Wright. Several guests (Drs. Conley, Ferry and Knisely) were invited to augment the original 16 workers in blood coagulation who met the previous year. Six new papers were presented and discussed. The problem

of the standardization of thromboplastin for prothrombin assays was reviewed without any satisfactory agreement.

The presentations of Dr. Tocantins' "The Separation and Assay of a Lipid Antithromboplastin from Human Brain, Blood Plasma and Plasma Fractions" and Dr. Overman's "The Chemical Purification and Mode of Action of Thromboplastin Inhibitor" while overlapping represent a revival of earlier researches in an effort to reinvestigate the problem. Many pertinent details were presented regarding thromboplastin and inhibitors.

Dr. Ferry's paper, "Consideration of the Structure and Mechanism of Formation of the Fibrin Clot," was a discussion of physicochemical aspects based on his own work. This lucid presentation elicited prolonged discussion of the fibrin network and the forces which bring fibrinogen molecules together.

Dr. Knisely introduced his discussion with a poem and then proceeded to elaborate on the phenomenon of blood sludging and the definition of "clot."

The platelets came in for their share of the program. Dr. Barker surveyed the difficult problem of the "Surface Effects on Blood Coagulation" in a scholarly presentation. He pointed out that the coagulation time of whole blood may vary considerably depending on the surface of the containers into which it is drawn even when other factors are kept as constant as possible. The use of silicone surfaces was discussed. Following this presentation Dr. Ferguson reviewed at length his own work with platelets and their properties. Dr. Quick reëmphasized his views of the importance of platelets in the mechanism of blood coagulation. He stated that there were three distinct functions for this formed element of the blood: (1) participation in the formation of thrombin, (2) formation of white thrombi to serve as plugs, and (3) vasoconstriction. He presented the position of platelets in the scheme of blood coagulation with new fanciful names and speculative enzyme entities. This presentation elicited a heated discussion by Drs. Brinkous and Ferguson on the problem of platelet-plasma reaction.

Dr. Wright introduced the subject of "Zeta-Potential Studies" in relation to clotting phenomena. These studies were of a preliminary nature.

A new synthetic anticoagulant was discussed by Dr. Wright. The material is a polysulfuric ester derivative of alginic acid known as Paritol. Side reactions were presented. Dr. Link presented his experiences with a similar series of derivatives and stated that there is a strong tendency for platelet agglutination with resultant infarction of lungs and kidneys.

Divergence of opinion and adherence to fixed concepts was still the theme during the conference. Many controversial points were aired but few clarified. Little if any advance was made in the elucidation of the mechanism of blood coagulation.

C. E. B.

Bone and Joint Radiology. By EMERIK MARKOVITS, M.D., formerly Scientific Collaborator of the Central Radiologic Institute of the General Hospital (Holzknecht-Institute), Vienna; Head of the Radiologic Department of Elizabeth Hospital of the City of Budapest; Postgraduate Lecturer of the Central Radiologic Institute of the University of Budapest; Radiologist of the Steiner Cancer Clinic, Atlanta, Ga. 446 pages; 18 × 26 cm.; 616 illustrations. The Macmillan Company, New York. 1949. Price, $20.00.

The specialty of radiology is profoundly indebted to many eminent European radiologists for their outstanding and accurate radiologic observations and descriptions of disease. The author describes his book as an "epitome of radiologic experiences covering a twenty-five year period." These experiences have, no doubt, been de-

veloped and colored by the teachings of the great European radiologists, and these teachings have been well amalgamated with those of the American continent. The truth is the same the world over, however much points of stress and interest vary from continent to continent.

The book is truly an epitome for it contains in the first part concentrated information about more than 140 conditions. The second part contains information and description of diseases affecting the bones and joints on a regional basis, yet all conditions mentioned are fully covered, either in one part or the other.

Part I has been divided into sections on the anatomy, physiology and radiologic anatomy of bones and joints; diseases of bones; diseases of joints; and diseases of muscles and soft tissues. Radiologic anatomy is stressed throughout the book, particularly in the second part where disease of bones and joints is considered from a regional standpoint. In this part of the book, chapters are devoted to the skull, the spine, the pelvis and hip joints, the femurs, the knee joint, the tibia and fibula, the ankle joint, the tarsal and metatarsal bones and phalanges of the foot, the thorax, the shoulder joint, the humerus, the elbow joint, the radius and ulna, the wrist joint and finally the carpal and metacarpal bones and the phalanges of the hand.

Many well-drawn diagrams are used to demonstrate characteristics of disease. The tables of classification, differential diagnosis and of growth and development make the book particularly desirable for the resident and young roentgenologist.

The reproduced radiographs are strikingly illustrative and are well selected. They would be more impressive if all were printed as positives of the x-ray films. The text is remarkably up-to-date with such recently described diseases as osteitis pubis, infantile cortical hyperostosis and osteoid osteoma included.

The bibliography is quite complete, and the indexing seems satisfactory. The paper, printing and binding are of a quality expected from the printers who have attained such perfection in this field.

The tabulation of information, the arrangement of material, the labelling of sections, the elimination of the questionable and the inclusion of only the essential has resulted in a book that should be found in the library of every roentgenologist.

W. L. K.

Sir William Osler: Aphorisms from His Bedside Teachings and Writings. Collected by Robert Bennett Bean, M.D.; Edited by William Bennett Bean, M.D. 158 pages; 10.5 × 16 cm. Henry Schuman, Inc., New York. 1950. Price, $2.50.

We all know that Sir William Osler was great in many ways—as a clinician, as a teacher, as a writer, as a personality. He might well be called the Hippocrates of the twentieth century, but he never published a collection of his own aphorisms. It has been left to the son of his late amanuensis, Robert Bean, to accomplish this worth while task. The apothegms in this pocket-sized volume were largely collected by Robert Bean on ward rounds with Osler between 1903 and 1905, and were committed to his notebook there and then—in obedience to one of Osler's own precepts, "make a note at the time; do not wait."

The purposes of this book are to introduce Osler to a new generation of medical students, to refresh the memory of an older generation, and to stimulate further exploration of the man and his writings. Aphorisms have a unique value in that they make their contained message immediately and effortlessly memorable; they are indeed "burrs that stick in the memory." We may be thankful therefore that Osler, who had so much to say, was master of the "succinct phrase and deft epitome." For his sayings of half a century ago are as timely today as they were then—thanks to

what Dr. Fulton in his foreword calls "the timeless character of Sir William's prose and precepts."

Since reading this little book, the reviewer has been impressed (and so have his tolerant companions) how frequently in the course of everyday conversation and activities a tag of Osler's is supremely *à propos*. It seems that he has contrived to distil a proverb for each and every one of life's contingencies, big and small, medical and nonmedical. From his playful admonition "choose a frecklefaced girl for a wife; they are invariably more amiable," to his serious thoughts on medical teachings and clinical medicine, his epigrams will well repay study. This is one of those rare books that fall into Bacon's third category, "to be chewed and digested."

There is no doubt that this anthology of philosophical gems, if it be as fully and widely appreciated as it deserves, will achieve the dual purpose of disseminating wisdom and keeping a great man's memory alive.

H. J. L. M.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

An Atlas of Human Anatomy. By BARRY J. ANSON, Ph.D., Professor of Anatomy, Northwestern University Medical School. 518 pages; 28.5 × 20.5 cm. 1950. W. B. Saunders Company, Philadelphia. Price, $11.50.

Disorders of the Blood: Diagnosis: Pathology: Treatment: Technique. 6th ed. By SIR LIONEL E. H. WHITBY, C.V.O., M.C., M.A., M.D. (Cantab.), F.R.C.P. (Lond.), D.P.H., Regius Professor of Physic in the University of Cambridge, etc.; and C. J. C. BRITTON, M.D. (New Zealand), D.P.H., Physician and Haematologist to the Prince of Wales's Hospital, London, etc. 759 pages; 25 × 16 cm. 1950. The Blakiston Company, Philadelphia. Price, $3.00.

Evaluation of Industrial Disability. Prepared by the Committee for Standardization of Joint Measurements in Industrial Injury Cases of the California Medical Association and Industrial Accident Commission, State of California. 89 pages; 24 × 16 cm. 1950. Oxford University Press, New York. Price, $4.00.

Freud: Dictionary of Psychoanalysis. Edited by NANDOR FODOR, Associate of the Association for the Advancement of Psychotherapy, and FRANK GAYNOR, co-author of the "Dictionary of Industrial Psychology"; with a Preface by THEODOR REIK, author of "Listening with the Third Ear." 208 pages; 22 × 14 cm. 1950. Philosophical Library, New York. Price, $3.75.

Grundsätzliches zur Diabetestherapie. By PROFESSOR DR. F. BERTRAM. 40 pages; 21 × 14.5 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, New York. Price, Kartoniert DM. 1.–

Immortal Magyar: Semmelweis, Conqueror of Childbed Fever. By FRANK G. SLAUGHTER, M.D. 211 pages; 21.5 × 14.5 cm. 1950. Henry Schuman, New York. Price, $3.50.

Lehrbuch der Inneren Medizin. By DR. ERNST LAUDA. 624 pages; 25 × 17 cm. 1949. Springer-Verlag, Vienna. Price, $3.10.

The 1950 Year Book of Medicine (May, 1949–May, 1950). Edited by PAUL B. BEESON, M.D., J. BURNS AMBERSON, M.D., WILLIAM B. CASTLE, M.D., S.M. (Hon.) Yale, M.D. (Hon.) Utrecht, TINSLEY R. HARRISON, M.D., and GEORGE

B. EUSTERMAN, M.D. 819 pages; 20 × 13.5 cm. 1950. The Year Book Publishers, Chicago. Price, $5.00.

O Que O Diabético Deve Saber. By DR. FRANCISCO ARDUINO. 106 pages; 23 × 16 cm. (paper-bound). 1950. Gráfica Santa Cecilia, Brazil. Price, $3.00.

Sir William Osler: Aphorisms from His Bedside Teachings and Writings. Collected by ROBERT BENNETT BEAN, M.D. (1874–1944); Edited by WILLIAM BENNETT BEAN, M.D. 158 pages; 16 × 10.5 cm. 1950. Henry Schuman, Inc., New York. Price, $2.50.

Principles of Internal Medicine. T. R. HARRISON, Editor-in-Chief. Editors: PAUL B. BEESON, WILLIAM H. RESNIK, GEORGE W. THORN and M. M. WINTROBE. 1590 pages; 27 × 19 cm. 1950. The Blakiston Company, Philadelphia. Price, $12.00.

Renal Diseases. 2nd ed. By E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis. 448 pages; 24 × 15.5 cm. 1950. Lea & Febiger, Philadelphia. Price, $8.00.

Reports on Biological Standards: VI. The Design of Toxicity Tests. By W. L. M. PERRY. 50 pages; 24.5 × 15 cm. (paper-bound). 1950. His Majesty's Stationery Office, London. Price, 1s 6d net.

Santa Claus, M.D. By W. W. BAUER, M.D. 266 pages; 21 × 14.5 cm. 1950. The Bobbs-Merrill Company, Inc., New York. Price, $2.75.

Serology with Lipid Antigen, with Special Reference to Kahn and Universal Reactions. By REUBEN L. KAHN, M.S., D.Sc., Associate Professor in Department of Dermatology and Syphilology, University of Michigan Medical School, etc. 327 pages; 23.5 × 15.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $6.00.

A Symposium on Steroid Hormones. Edited by EDGAR S. GORDON, with Contributions by S. A. ASDELL, S. BIRD, JOHN J. BITTNER, KONRAD BLOCH, H. H. COLE, NICHOLAS E. COLLIAS, KONRAD DOBRINER, L. V. DOMM, LOUIS F. FIESER, THOMAS F. GALLAGHER, ROY O. GREEP, HANS HIRSCHMANN, FREDERICK L. HISAW, CHARLES B. HUGGINS, R. R. HUMPHREY, ROBERT A. HUSEBY, DWIGHT J. INGLE, I. CHESTER JONES, CHARLES D. KOCHAKIAN, SEYMOUR LIEBERMAN, F. W. LORENZ, G. F. MARRIAN, HAROLD L. MASON, CARL R. MOORE, EDWARD C. REIFENSTEIN, JR., LEO T. SAMUELS, J. J. SCHNEIDER, ULRICH V. SOLMSSEN, CHARLES W. TURNER, GRAY H. TWOMBLY, ELEANOR H. VENNING, ALBERT WETTSTEIN, ABRAHAM WHITE, and ALFRED L. WILDS. 396 pages; 24 × 16 cm. 1950. The University of Wisconsin Press, Madison. Price, $6.50.

Therapeutic Radiology. By GEORGE WINSLOW HOLMES, M.D., Radiologist, Waldo County General Hospital, Maine, etc.; and MILFORD D. SCHULZ, M.D., Radiologist, Massachusetts General Hospital, etc. 347 pages; 24 × 15.5 cm. 1950. Lea & Febiger, Philadelphia. Price, $7.50.

COLLEGE NEWS NOTES

Postgraduate Courses, American College of Physicians

There were nine short, intensive postgraduate courses on the Autumn, 1950, schedule, five of which have already been concluded. In each instance, the courses given were either over-subscribed or more than the minimal quota reached.

Course No. 6, PERIPHERAL VASCULAR DISEASES INCLUDING HYPERTENSION, under the direction of Dr. Walter F. Kvale, Mayo Clinic and Mayo Foundation, Rochester, Minn., opens on November 27 and has been over-subscribed.

The remaining courses are as follows:

Course No. 7, GASTRO–ENTEROLOGY; Henry L. Bockus, M.D., F.A.C.P., Director; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; December 4–9, 1950.

This course may be greatly over-subscribed and anyone who desires to register should inquire immediately about vacancies available.

Course No. 8, SELECTED ASPECTS OF CLINICAL HEMATOLOGY; William Dameshek, M.D., F.A.C.P., Director; New England Center Hospital and Tufts College Medical School, Boston, Mass.; December 11–16, 1950.

Course No. 9, MODERN TRENDS IN DIAGNOSIS AND TREATMENT OF HEART DISEASE; William G. Leaman, Jr., M.D., F.A.C.P., Director; Woman's Medical College of Pennsylvania and other Philadelphia institutions, Philadelphia, Pa.; January 22–27, 1951.

The Advisory Committee on Postgraduate Courses met at the Headquarters of the College on November 11, 1950, to formulate the program for 1951. The schedule adopted will appear in the next issue of this journal.

Regional Meetings

Regional meetings during the Autumn of 1950 have already been concluded in North Dakota, Montana, Wyoming, Western Pennsylvania, Mississippi, Northern California, Southern California, Arizona, Western New York, The Northwestern States and Western Provinces of Canada, New Jersey, Puerto Rico, Utah, the Midwestern States of Illinois, Indiana, Iowa, Michigan, Minnesota, Ohio and Wisconsin. Other regional meetings officially scheduled include:

North Carolina, at Chapel Hill, December 8, 1950.
Kentucky, at Lexington, December 9, 1950.
Mid-South (Tennessee, Texas and Louisiana), at Memphis, January 12–13, 1951.
Southeastern (South Carolina, Georgia, and Florida), at Charleston, S. C., January 26–27, 1951.
Colorado, at Denver, February 20, 1951.
Delaware, at Wilmington, February 22, 1951.
Kansas, at Wichita, March 16, 1951.

Other regional meetings definitely planned include Nebraska, at Omaha, and Maryland and the District of Columbia, at Washington.

Programs of the regional meetings customarily are mailed only to the members in the area for which the regional meetings are organized, but any member, by request to the Executive Secretary of the College, may be furnished with any or all of the regional meeting programs.

100th Annual Session, the Medical Society of the State of Pennsylvania

The 100th Annual Session of the Medical Society of the State of Pennsylvania was held in Philadelphia, October 15–19. Among the guest speakers on the program were: Dr. Charles S. Davidson, F.A.C.P., Boston, Mass., "The Internist's View of the Treatment of Liver Disease"; Dr. Irving S. Wright, F.A.C.P., New York, N. Y., "The Use and Abuse of Anticoagulant Drugs"; Dr. Russell L. Cecil, F.A.C.P., New York, N. Y., "Treatment of Rheumatoid Arthritis"; Dr. George A. Wolf, Jr. (Associate), New York, N. Y., "Headache"; Dr. Will C. Spain, F.A.C.P., New York, N. Y., "The Case for Histamine as the Basis of Allergic Reactions: Attempts at Its Neutralization"; Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y., "Medical Aspects of Regional Ileitis"; and Dr. Clayton B. Ethridge, F.A.C.P., Washington, D. C., "Diagnosis and Therapy in Various Forms of Coronary Heart Disease."

One of the features of the Session was the Installation Meeting, held on October 17, when Dr. Harold B. Gardner, Pittsburgh, Pa., was installed as President of the Society. At this meeting 373 society members who have completed the three-year course of the Graduate Education Institute of The Medical Society of the State of Pennsylvania were presented certificates. Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., addressed the meeting on "Keeping Abreast of Medical Progress."

The Scientific Exhibit, held in conjunction with the session, included forty-two displays, many of which were presented by Fellows and Associates of the College. These included: Dr. Ella Roberts, F.A.C.P., Philadelphia, Pa., "Ten Years' Experience with Sulfonamides in the Prophylaxis of Rheumatic Fever"; Dr. Charles H. Dewan, F.A.C.P., and Dr. Paul L. Shallenberger (Associate), both of Sayre, Pa., (with Drs. C. B. Weed and J. C. Reganis), "Gastroscopic Biopsy"; Dr. Harrison F. Flippin, F.A.C.P., and Dr. William P. Boger, F.A.C.P., both of Philadelphia, (with Dr. W. V. Matteucci), "'Benemid,' a Compound Influencing Metabolism of Penicillin and Para-aminosalicylic Acid"; Dr. Burgess L. Gordon, F.A.C.P., Philadelphia, (with Drs. H. L. Motley, P. A. Theodos, L. P. Lang and J. F. Tomashefski), "Anthracosilicosis"; Dr. Horst A. Agerty, F.A.C.P., Philadelphia, (with Drs. R. M. Bernardin and W. C. Foster), "Lead Poisoning in Children"; Dr. Mildred C. J. Pfeiffer, F.A.C.P., Philadelphia, "Newer Aids in Cancer Diagnosis"; Dr. Frederick O. Zillessen, F.A.C.P., Philadelphia, (with Drs. A. E. Bothe and A. J. Dalton), "A Study of the Golgi Material and Mitochondria in Neoplasms of the Kidney, Urinary Bladder, and Prostate"; and Dr. C. Wilmer Wirts, F.A.C.P., Philadelphia, (with Drs. R. L. Breckenridge, S. D. Kusterman and D. M. Wald), "Gastric Biopsy with the Operating Gastroscope."

The Virginia State Section of the American College of Physicians held a luncheon meeting at the Patrick Henry Hotel in Roanoke, Va., on October 10, during the meeting of the Medical Society of Virginia. Dr. J. Franklin Waddill, F.A.C.P., of Norfolk, is the Secretary of the Virginia Section. Dr. Charles Caravati, F.A.C.P., of Richmond, is the College Governor for Virginia.

New Life Member

The College is gratified to announce that Dr. Aloysius J. Connolly, Washington, D. C., has become a Life Member of the American College of Physicians since the publication of the last issue of this journal.

The Eastern Sectional Meeting of the American Federation for Clinical Research will be held on December 9, 1950 in the Main Auditorium of the Army Medical School, Walter Reed Hospital, Washington, D. C.

The 1950 Convention of The Association of Military Surgeons of the United States was held from November 9 to November 11, inclusive, at the Hotel Statler, New York City.

Appropriate to the times, the programs dealt with Civil Defense, the Defense Rôle of the Physician, Aviation Medicine, Rehabilitation, Military Medicine, Surgery, Sanitation, and discussions on the use of the newest therapeutic and prophylactic agents in emergency conditions. Several of the sessions were directed to the problems of the Medical Reserve.

Fellowships in Industrial Medicine

The Institute of Industrial Health of the University of Cincinnati will accept applications for a limited number of Fellowships which are being offered to qualified candidates who wish to pursue a graduate course of instruction which will qualify them for the practice of Industrial Medicine. Candidates who complete satisfactorily the course of study will be awarded the degree, Doctor of Industrial Medicine. Any registered physician, who is a graduate of a Class A medical school and who has completed satisfactorily two years of residency (including internship) in a hospital accredited by the American Medical Association, may apply for a Fellowship in the Institute of Industrial Health. The course of instruction consists of a two-year period of intense preliminary training in the basic phases of Industrial Medicine followed by one year of practical experience under adequate supervision in industry. During the first two years, the stipends for the Fellowships vary from $2,100 to $3,000. In the third year the candidate will be compensated for his service by the industry in which he is completing his training. Requests for additional information should be addressed to the Institute of Industrial Medicine, University of Cincinnati College of Medicine, Cincinnati 19, Ohio.

Fellowships in Allergy Available at Northwestern University Medical School

Two fellowships in allergy are available for 1951 at Northwestern University Medical School. These fellowships are of one-year duration and include clinical and investigative experience. Preference will be given to those who have or intend to complete their board requirements in internal medicine or pediatrics. The stipend is $2,400 to $3,600. Further information may be obtained from Dr. Samuel M. Feinberg, F.A.C.P., Northwestern University Medical School, Chicago 11, Ill.

University of Pennsylvania Stimulates Graduate Research in the Physical, Biological and Medical Sciences

To stimulate graduate research and instruction programs in the educational area which overlaps the physical, biological and medical sciences, an Interscience Commission has been organized at the University of Pennsylvania and is now functioning in the first academic year of its existence. The announcement states that the program was initiated because of a general recognition of the growing need for closer interaction between workers in the physical sciences and engineering on the one hand and those in the biological and medical sciences on the other hand. Because modern research in the biological-medical sciences requires for effective attack the technics and interpretations of the physical sciences, it was explained, investigators in these

fields increasingly need fundamental training in the physical sciences. At the same time workers in the physical sciences today are finding enhanced opportunities for research in the biological-medical field.

Only students of high caliber, willing to devote four years of full-time study to doctoral programs, are encouraged to elect the new area of specialized study, according to the University's announcement. Programs are varied to meet individual needs after consultation with various University officials. The programs lead to the final award of a Ph.D. degree.

New Dean of University of Pennsylvania Graduate School of Medicine

On October 3, the University of Pennsylvania announced the appointment of Dr. Aims C. McGuiness as Dean of the University of Pennsylvania Graduate School of Medicine to assume office on January 1, 1951. Dr. McGuiness has been Director of the Children's Hospital of Philadelphia since 1948. He is a graduate of the Columbia University College of Physicians and Surgeons, 1931. He served his internship with the Hospital of the University of Pennsylvania and his residency at the Children's Hospital of Philadelphia. Since 1946, he has been Assistant Professor of Pediatrics at the University of Pennsylvania School of Medicine. During World War II he served as a Lieutenant Colonel in the Medical Corps of the U. S. Army.

The vacancy was caused by the resignation of Dr. William S. Parker who will devote his full time in the future to the practice of surgery.

Dr. Edward C. Reifenstein, Jr., Named Director of the Research Institute of the Oklahoma Medical Research Foundation

Dr. Edward C. Reifenstein, Jr., F.A.C.P., New York City, has been named Director of the Research Institute of the Oklahoma Medical Research Foundation to assume office November 1, 1950.

A strikingly beautiful and ultra-modern $1,000,000 Foundation home has been completed recently adjacent to the University of Oklahoma School of Medicine in Oklahoma City. Special laboratory equipment is being installed and research activities start at once.

Dr. Reifenstein graduated from Syracuse University College of Medicine in 1934. For several years he was associated in practice with his father, specializing in internal medicine and psychiatry. He later joined Dr. Fuller Albright at the Massachusetts General Hospital in Boston, spending six years with him doing advanced research in endocrinology and metabolic bone disorders. Since 1946 Dr. Reifenstein has been Consultant and later Research Associate at the Sloan-Kettering Institute, where he has conducted investigations on the endocrine aspects of cancer. For the past four years he has also been Consultant and later Executive Director of the Medical and Research Division of Ayerst, McKenna and Harrison, Ltd., manufacturing pharmacists.

Edgar Hull, M.D., F.A.C.P., New Orleans, 2nd Vice-President of the American College of Physicians and Professor of Medicine and Head of the Department, Louisiana State University School of Medicine, was awarded a Fulbright Teaching Fellowship, as Lecturer in Medical Sciences at the University of Bologna. Dr. Hull left during October and will not return to this country until June, 1951.

The Annual Scientific Assembly of the Medical Society of the District of Columbia was held in Washington, October 2-4, under the Presidency of Dr. Wil-

liam M. Ballinger, F.A.C.P. Visiting speakers were Dr. Louis J. Soffer, F.A.C.P., New York, "ACTH and Cortisone: The Present Status of Their Rôle in Clinical Medicine"; Dr. Cornelius P. Rhoads, F.A.C.P., New York, "Advances in the Chemotherapy of Neoplastic Diseases," and Dr. William A. Sodeman, F.A.C.P., New Orleans, "Advances in Diagnosis and Treatment of Amebiasis."

Among the speakers at the Annual Meeting of the Oregon State Medical Society held in Gearhart, September 27–30, were Dr. Thomas A. Johnson, F.A.C.P., Philadelphia, Pa., "Diagnosis and Management of Pancreatic Disease," and Dr. Henry W. Woltman, F.A.C.P., Rochester, Minn., "Differential Diagnosis of Poliomyelitis."

A one-day course in the use of ACTH and Cortisone, sponsored by the Kanawha Medical Society, was held in Charleston, W. Va., on October 4. Among the speakers were Dr. David E. Markson, F.A.C.P., Associate Professor of Medicine at the Northwestern University Medical School, and Dr. Theron G. Randolph (Associate), Instructor in Medicine at Northwestern University.

The opening address at the Annual Meeting of the Association of American Medical Colleges which was held at the Lake Placid Club, Essex County, N. Y., October 23–25, was Dr. Howard A. Rusk, F.A.C.P., New York, N. Y. Dr. Rusk's subject was "Medical Manpower in Time of Emergency."

Dr. James H. Means, F.A.C.P., Jackson Professor of Clinical Medicine, Harvard Medical School, and Physician in Chief, Massachusetts General Hospital, delivered the Third Annual Harvard Lecture at the University of Colorado Medical Center on October 27, his subject being "Integrative Action of the Endocrine System."

Thirteen Fellows of the College were included on the Visiting Faculty for two postgraduate courses presented recently by the Chicago Medical Society. "Diseases of the Gastrointestinal Tract, Liver and Pancreas" was given October 23–27; "Diseases of the Heart, Kidneys and Blood Vessels" was given October 30 to November 3. The following physicians, all Fellows of the College, were included on the Faculty; George B. Eusterman, Rochester, Minn.; John H. Fitzgibbon, Portland, Ore.; Walter C. Alvarez, Rochester, Minn.; Russell S. Boles, Philadelphia, Pa.; Leon Schiff, Cincinnati, Ohio; Robert L. Levy, New York, N. Y.; Irving S. Wright, New York, N. Y.; A. Carlton Ernstene, Cleveland, Ohio; William H. Bunn, Youngstown, Ohio; Edgar A. Hines, Jr., Rochester, Minn.; Eugene A. Stead, Jr., Durham, N. C.; Francis D. Murphy, Milwaukee, Wis., and Howard B. Sprague, Boston, Mass.

Dr. Leon J. Galinsky, F.A.C.P., Des Moines, was recently elected President of the Iowa Trudeau Society.

Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y. and Dr. Franklin G. Ebaugh, F.A.C.P., Denver, Colo., were among the guest speakers at the Annual Assembly of the Omaha Mid-West Clinical Society held in Omaha, October 23–27.

The Nevada State Medical Association held its Annual Meeting in Las Vegas, October 5–7. Among the guest speakers were Dr. Travis Winsor, F.A.C.P., Los Angeles, Calif., who spoke on "Diagnosis and Treatment of Peripheral Vascular

Disease," and Dr. Howell S. Randolph, F.A.C.P., Phoenix, Ariz., who spoke on "Masquerades of Pulmonary Malignancies."

Dr. E. Herndon Hudson, F.A.C.P., Director of the Ohio University Health Service, was appointed Director and Chief Medical Adviser of the United Nations World Health Organization project in Iraq, which started October 1. The project, which is devoted to the study and treatment of bejel, a disease prevalent among children in that country, is sponsored jointly by the World Health Organization and the Iraq government. The Iraq government is furnishing a trailer, outfitted so that Dr. Hudson may make a self-sustaining expedition into the desert. It is planned to examine and test up to 70,000 persons in the course of a year and to establish treatment and control procedures that may be continued later by the government.

At the Organization Meeting of the West Virginia Diabetes Association held in White Sulphur Springs on July 29, Dr. George P. Heffner, F.A.C.P., Charleston, was elected President. Dr. William M. Sheppe, F.A.C.P., Wheeling, was named President-elect.

Among the speakers at the Annual Meeting of the College of American Pathologists, held in Chicago October 16–17, was Colonel Albert DeCoursey (MC), USA, F.A.C.P., Washington, D. C.

Dr. Chester N. Frazier, F.A.C.P., Boston, Mass., was recently elected Director of the Society for Investigative Dermatology.

The American Congress of Physical Medicine has elected Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., Treasurer. Dr. George Morris Piersol, M.A.C.P., Philadelphia, Pa., was appointed to serve a term of six years on the Editorial Board of the *Archives of Physical Medicine.*

The Central Neuropsychiatric Association held its Annual Convention October 13–14 in Cleveland. Included in the program of speakers were Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, Ohio, who spoke on, "Porphyria," and Dr. Edward O. Harper (Associate), also of Cleveland, Ohio, who spoke with Dr. Paul A. Mattis, Sc.D. on, "Comparison of the Uptake of Radioactive Thyroxine by the Tuber Cinereum, Hypophysis and Thyroid."

Dr. Elmer C. Bartels, F.A.C.P., Boston, Mass., was one of the guest speakers at the Annual Assembly of the U. S. Chapter of the International College of Surgeons held in Cleveland, Ohio, October 31–November 3. Dr. Bartels' subject was "Preoperative Use of Antithyroid Drugs."

Dr. Virgil P. Sydenstricker, M.A.C.P., Augusta. Professor of Medicine at the Medical College of Georgia, was recently appointed Medical Consultant to the Georgia Training School for Mental Defectives at Gracewood.

Among the guest speakers at the Georgia Heart Association's Second Annual Meeting held in Atlanta, September 15 and 16, under the Presidency of Dr. T. Sterling Claiborne, F.A.C.P., Atlanta, were three Fellows of the College and one Associate. They were: Dr. Tinsley R. Harrison, F.A.C.P., Birmingham, Alabama,

"Unusual Aspects of Chest Pain"; Dr. Edgar Hull, F.A.C.P., New Orleans, La., "The Choice of Leads in Clinical Electrocardiography"; Dr. Eugene B. Ferris, F.A.C.P., Cincinnati, Ohio, "The Diagnosis and Management of Hypertension"; and Dr. John P. Merrill (Associate), "The Rôle of The Artificial Kidney in Cardiovascular Diseases."

At the meeting of the American Board of Internal Medicine in San Francisco, Dr. Hugh R. Butt, F.A.C.P., Rochester, Minn., was elected a member of the Subspecialty Board in Gastro-enterology as a representative of the American Gastroenterological Association. Dr. Lowell D. Snorf, F.A.C.P., Evanston, Ill., was elected to the Subspecialty Board to represent the section on Gastroenterology and Proctology of the American Medical Association.

Among the speakers at the annual meeting of the American Academy of Ophthalmology and Otolaryngology held in Chicago, October 8–13, were Dr. Wesley W. Spink, F.A.C.P., Minneapolis, Minn., and Dr. Howard F. Polley (Associate), Rochester, Minn. Dr. Spink's subject was "Human Brucellosis," and Dr. Polley's subject was "The Collagen Diseases."

Dr. Abraham M. Kleinman, F.A.C.P., Chief of Professional Services at the Veterans Administration Hospital, Brooklyn, N. Y., has been appointed Clinical Associate Professor of Medicine at the State University Medical Center at New York City, College of Medicine for the Academic Year 1950–1951.

The following Fellows of the College were included on the program of the annual meeting of the Association of Life Insurance Medical Directors held in New York, N. Y., October 19–20: Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn.; Dr. William Dock, F.A.C.P., Brooklyn, N. Y.; Dr. Hugh B. Campbell, F.A.C.P., Hartford, Conn.; Dr. Roy W. Scott, F.A.C.P., Cleveland, Ohio; and Dr. Richard S. Gubner, F.A.C.P., Brooklyn, N. Y.

Dr. Cotter Hirschberg (Associate), Denver, Colo., was recently appointed Director of the Mental Hygiene Clinic of the University of Colorado School of Medicine.

Among the speakers at the annual meeting of the Medical Society of Delaware, held in Dover, October 2–4, were six Fellows of the College, all of Philadelphia: Dr. David A. Cooper, F.A.C.P., "Antibiotic Therapy"; Dr. Joseph F. Hughes, F.A.C.P., "Treatment of Anxiety States"; Dr. Joseph B. Vander Veer, F.A.C.P., "Anticoagulant Therapy in Acute Myocardial Infarction, Venous Thrombosis and Pulmonary Embolism"; Dr. Rufus S. Reeves, F.A.C.P., "Tuberculosis in Small Communities"; Dr. William G. Leaman, Jr., F.A.C.P., "Rehabilitation After Acute Infarction"; and Dr. Edward L. Bortz, F.A.C.P., "Biology of Aging."

Dr. Robert H. Williams, F.A.C.P., Seattle, Wash., was among the guest speakers at the annual meeting of the Idaho State Medical Association, held in Sun Valley, September 5–8. His subject was "Pyelonephritis."

The University of Kansas School of Medicine has announced the promotion of Dr. Mahlon H. Delp, F.A.C.P., to the post of Professor of Medicine. Dr. Lee H.

Leger, F.A.C.P., Dr. Sloan J. Wilson, F.A.C.P., and Dr. Max S. Allen (Associate) were promoted to the rank of Associate Professors of Medicine. Dr. William H. Algie, F.A.C.P., was promoted to Assistant Professor of Medicine.

One of the featured speakers at the rural health conference, sponsored by the State Medical Society of Wisconsin and 55 farm, health, civic and governmental organizations, which met at Green Lake, Wis., September 22–23, was Dr. Charles L. Dunham (Associate) of the Atomic Energy Commission, Washington, D. C.

The Office of the Surgeon General, U. S. Army, has announced the assignment of commanding officers for station hospitals in recently reactivated Army camps. Colonel Mack M. Green (MC), USA, F.A.C.P., has been assigned as commanding officer of the Station Hospital, Camp Rucker, Ala., and Colonel Clifford A. Best (MC), USA, F.A.C.P., has been assigned as commanding officer of the Station Hospital, Fort Leonard Wood, Mo.

Promotions to full professorship in the Department of Medicine for Dr. Carroll L. Birch, F.A.C.P., and Dr. Ford K. Hick, F.A.C.P., were recently announced by the University of Illinois College of Medicine. Dr. Birch has been a member of the faculty since 1926 and Dr. Hick since 1931.

Dr. O. Spurgeon English, F.A.C.P., Professor and Head of the Department of Psychiatry, Temple University School of Medicine, spoke on "Psychosomatic Medicine and Dietetics" at the thirty-third annual meeting of the American Dietetic Association held in Washington, D. C., October 16–20.

Dr. Joseph B. Kirsner, F.A.C.P., Chicago, Ill., spoke on "Recent Therapeutic Advances in Gastrointestinal Disorders" at the meeting of the Dallas County (Tex.) Medical Society, September 12.

Among the guest speakers at the annual meeting of the Medical Society of Virginia, held in Roanoke, October 8–11, was Dr. Franklin D. Murphy, F.A.C.P., Kansas City, Kans. His subject was "Postgraduate Education for the Practicing Physician."

Dr. Yale Kneeland, F.A.C.P., New York, N. Y., spoke on "Advances in Treatment of Respiratory Diseases," at the annual meeting of the State Medical Society of Wisconsin held in Milwaukee, October 2–4.

Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., addressed the North Texas-Southern Oklahoma Fall Clinical Conference at Wichita Falls, Tex., on September 20, his subject being "Antibiotics in Common Use Today."

Dr. Adolph Sachs, F.A.C.P., Omaha, Nebr., was recently appointed Chairman of the Creighton University Board of Regents. He has been a Regent of that University since 1939. He is Professor of Medicine in the Medical School and for several years was the Governor of the American College of Physicians for Nebraska.

OBITUARIES

DR. NATHAN THOMAS BEERS

Dr. Nathan Thomas Beers, F.A.C.P., Brooklyn, N. Y., died on July 7, 1950. He was born in Brooklyn in 1874; received his M.D. degree from Long Island College Hospital in 1897 and served his internship in the Long Island College Hospital thereafter. He specialized in dermatology and at the time of his death was Consulting Dermatologist at the Brooklyn, Methodist, St. John's, Swedish, Carson C. Peck Memorial, Victory Memorial and St. Mary's Hospitals. He was also Consulting Dermatologist to the New York Police Department.

Dr. Beers was a Diplomate of the American Board of Dermatology and Syphilology and a member of the American Radium Society, Kings County Medical Society, New York State Medical Society and the American Medical Association. He had been a Fellow of the American College of Physicians since 1921. He was a distinguished dermatologist and public minded citizen.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. THOMAS JOSEPH LONGO

Thomas J. Longo, M.D., F.A.C.P., Brooklyn, N. Y., died on August 15, 1950, after a two months' illness at the age of 64 years. He was born in Italy, the son of a pharmacist. He, himself, practiced pharmacy in Brooklyn after graduating from the Board of Pharmacy Institute in 1904. In 1916 he graduated from Fordham University School of Medicine and thereafter pursued postgraduate courses and started in the practice of medicine in Brooklyn.

Dr. Longo was an Attending Physician at the Coney Island Hospital for the past 21 years, Director of Medicine there for the last 5 years, and President of the Hospital Medical Board for the last 3 years. He was also Consulting Physician at the Samaritan Hospital and Attending Physician at the Harbor Hospital in Brooklyn. He served also on the staffs of the Long Island College and Kings County Hospitals. He was a former Instructor of Medicine at Long Island College Hospital, a member of the Board of Visitors of the Creedmore State Hospital, Consultant in Cardiology for the State Insurance Fund, a Member of the State Advisory Board, and a Physician to the Selective Service System of World War II.

Dr. Longo had been a Fellow of the American College of Physicians since 1929. He was a member of the American Heart Association and numerous other medical organizations and belonged to the Montauk Club of Brooklyn. He was a Diplomate of the American Board of Internal Medicine. In addition to being a distinguished physician, Dr. Longo was interested in civic affairs and made an outstanding name for himself during his active life.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. WILLIAM HULBERT BARROW

William Hulbert Barrow, A.B., M.D., F.A.C.P., was born in Baltimore, Md., May 18, 1886, and died in Mercy Hospital, San Diego, Calif., on April 12, 1950, of coronary heart disease.

He received his A.B. degree from Harvard College in 1908 and graduated from Harvard Medical School in 1916. He served overseas during World War I with the United States Army Medical Corps, retiring in 1921 with the rank of Captain.

Dr. Barrow was formerly on the faculty of Stanford University School of Medi-

cine, San Francisco, from 1922 to 1928, where he served as Professor of Hygiene and Physical Education and Associate Clinical Professor of Medicine. He came to San Diego in 1928 and was in active practice there until his retirement in January, 1949. Until this time he was a member of the Senior Staff of the Mercy Hospital and a member of the Associate Staff of the Scripps Memorial Hospital.

Dr. Barrow was a member of the American Medical Association, American Heart Association and a past president of the Southern California Medical Association. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1930.

LELAND HAWKINS, M.D., F.A.C.P.,
Governor for Southern California

DR. DONALD W. W. STEWART

Dr. Donald W. W. Stewart, Associate of the American College of Physicians, died in the Peter Bent Brigham Hospital, Boston, on April 21, 1950, as the result of a coronary occlusion suffered while attending the 31st Annual Session of the College in that city.

Dr. Stewart was born in Saskatchewan, Canada, August 1, 1905. He graduated from the University of Saskatchewan, B.A., 1928, and from the University of Toronto School of Medicine, M.D., 1933. After spending a junior internship in the Riverdale Isolation Hospital he continued his graduate training at the Toronto Western Hospital where in 1936–37 he became my Assistant Resident. During this year Dr. Stewart impressed us with his professional skill, his industry and kindly human qualities.

Dr. Stewart joined the staff of the Sudbury (Ontario) Clinic in 1937 and at the time of his death was Chief of the Medical Staff of that organization. He was on the staff of St. Joseph's Hospital, Sudbury, and was Medical Consultant for the Canadian Pensions Commission and the Department of Veterans Affairs.

In 1945 Dr. Stewart became a Fellow of the Royal College of Physicians of Canada; he was a member of the American Heart Association, the Trudeau Society and the Canadian Rheumatism Association. He was elected an Associate of the American College of Physicians in 1946.

Dr. Stewart will be greatly missed not only in his district of Sudbury, where his excellent qualities as physician and citizen gained him the highest esteem, but also in the medical profession of Ontario where he was well known as an exceptionally able physician.

H. K. DETWEILER, M.D., F.A.C.P.,
Governor for Ontario

DR. GEORGE DALLAS HENDERSON, SR.

George Dallas Henderson, Sr., M.D., F.A.C.P., Holyoke, Mass., died June 15, 1950, at the age of 75, of lymphatic leukemia. He was born in Ohio on October 7, 1874, and received his medical degree in 1900 from Western Reserve University School of Medicine. He was Chief of the Medical Service, Holyoke Hospital, and Consultant in Internal Medicine, Belchertown State School and Westfield State Sanatorium. He held membership in the Holyoke and Tri-County (State) Medical Society and the Massachusetts Medical Association. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1932.

Dr. Henderson was a fine physician and a leader in his community who practiced medicine of the highest type. For many years he took an active part in postgraduate medical education in Massachusetts and served on the Committee on Medical Educa-

tion of the Massachusetts Medical Society. By example, he was responsible for maintaining the level of medical practice in his community on a very high level. One would often see Dr. Henderson at state and national medical meetings and his interest in modern advancement in medicine never lagged. His friends, patients and colleagues will always remember him for his devotion to duty and for his fine spirit as a good citizen and physician.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. EDWIN CHESTER SWIFT

Dr. Edwin Chester Swift, Captain, Medical Corps, U. S. Naval Reserve, last on duty at the U. S. Naval Hospital, Philadelphia, died at that hospital on June 4, 1950. Dr. Swift was born in Woodbine, Ga., October 15, 1900. He attended the University of Georgia and then entered the Emory University School of Medicine from which he received his medical degree in 1924. Prior to World War II, he was a member of the Medical Staff of the Brewster, St. Luke's, St. Vincent's, Riverside and Duval County Hospitals, at Jacksonville, Fla. He was later Medical Director of the Moosehaven Hospital, Orange Park, Fla.

Dr. Swift entered active service in the Medical Corps of the U. S. Naval Reserve in June, 1941, and was first assigned to the Naval Hospital at Jacksonville. Following retirement from active duty, he resumed his practice in Jacksonville during November, 1945, but in July, 1949, he re-entered upon active duty with the Navy and served as a member of the Medical Staff of the U. S. Naval Hospital at Philadelphia, with the rank of Captain.

Dr. Swift was a member of the Southern Medical Association, the Florida Medical Association, a Fellow of the American Medical Association and had served as Treasurer of the Duval County (Fla.) Medical Association and, as Secretary (1930–31), of the Florida East Coast Medical Association. He had been a Fellow of the American College of Physicians since 1933.

DR. AARON EPHIM PARSONNET

Aaron Ephim Parsonnet, M.D., F.A.C.P., died of coronary thrombosis on August 20, 1950. He was a man who became not only an outstanding physician but was widely recognized in many other fields. Born in Balta, Russia, September 15, 1888, and educated in Newark and at Loyola University School of Medicine, Chicago, he started to teach while still a student. He continued as a lecturer in electrocardiography at the Third Naval District and in short courses at Harvard, Johns Hopkins and the University of Michigan. His teaching rounds were an oustanding contribution and delight to his students for many years.

From his internship at the old Newark Beth Israel Hospital, he rapidly advanced to become Attending Physician in Medicine at that institution, which position he maintained for many years. In addition, he was Consulting Cardiologist for the home office of the Prudential Life Insurance Company, West Hudson Hospital in Kearny, Aurora Institution in Morristown, Perth Amboy General Hospital and St. Elizabeth Hospital in Elizabeth, N. J.

Dr. Parsonnet was the author of two books and of more than fifty papers on medical subjects. "Insulin Angina," "Herpes Zoster and Angina Pectoris," and "Myocardosis" were among outstanding contributions he made to the advancement of medical thought. Dr. Parsonnet had many hobbies, including the collection of Russian silver, books and stamps, also the designing of medical magazine covers and medical fraternity pins. Bookbinding was another of his hobbies, and some of his

work was so outstanding as to result in his receiving a special prize at one of the American Medical Association annual meetings. He also had taken to oil painting, where again his skill was recognized by first prizes in 1947 and in 1949.

During World War I Dr. Parsonnet was active at Port Newark for the Navy. In 1935 he helped organize a Naval Reserve Unit in Northern New Jersey, and was on active naval duty before Pearl Harbor, serving a short period as Lieutenant Commander. Thereafter he organized and headed a Public Health Service Unit as Senior Surgeon and had a short tour of duty at Halloran General Hospital. Dr. Parsonnet was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1924. He conducted an active cardiologic practice in Newark.

ARTHUR BERNSTEIN, M.D., F.A.C.P.

DR. KENNETH PAUL HOEL

Kenneth Paul Hoel, M.D., F.A.C.P., Aurora, Illinois, died July 4, 1950, at the age of 44, of coronary thrombosis. He was born in Baldwin, Wisconsin, December 24, 1905, and received his A.B. (1927) and M.D. (1929) degrees at the University of Wisconsin. His internship and residency were served at the University of Kansas Hospitals, Kansas City, Kans. Following this, he entered private practice in Wisconsin and later served on the staffs of The Wisconsin State Tuberculosis Sanitarium and The Oaks Sanitarium at Pewaukee, Wisconsin. In 1942, Dr. Hoel moved to Aurora, Illinois, where he again resumed the private practice of Internal Medicine. There he was an active staff member of Copley Memorial, St. Joseph Mercy and St. Charles Hospitals, and had served as President of the Staff at the latter two institutions.

Dr. Hoel was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1942. He was also a member of the Wisconsin State Medical Society, American Trudeau Society and the American Heart Association.

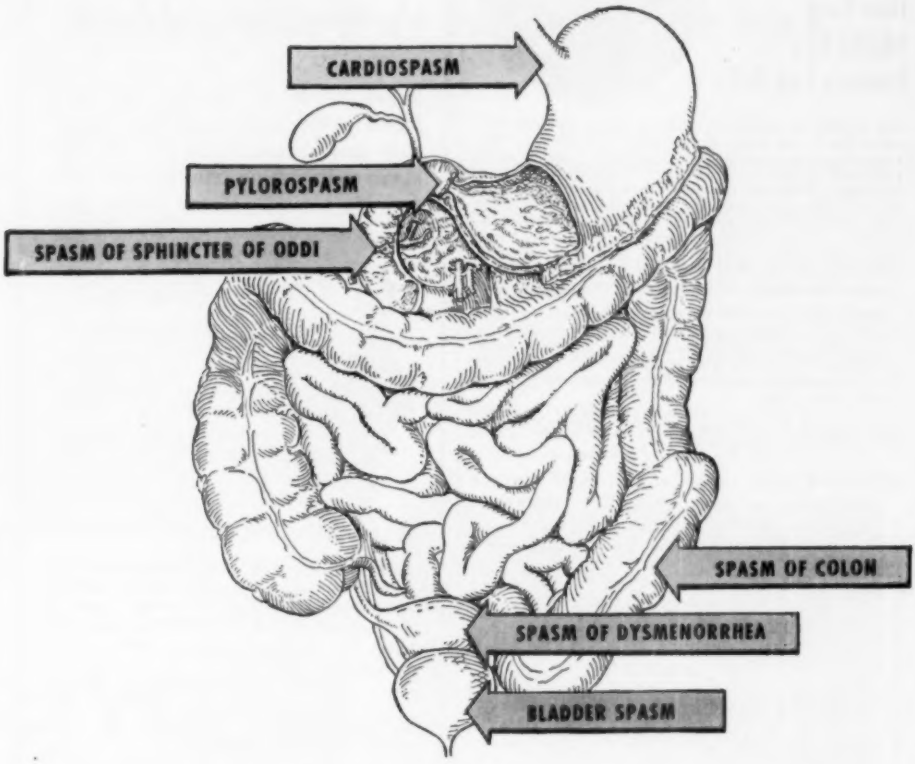
His untimely death took from our ranks a very conscientious clinician whose chief interest was the care of his very large practice. His patients not only respected him for his ability and consideration but each felt that Dr. Hoel was his close personal friend. He is remembered as a quiet, serious physician who gave unsparingly of his medical knowledge and perhaps too much of his physical strength.

C. L. GARDNER, M.D., F.A.C.P.

DR. CHARLES ARTHUR WATERBURY

Charles Arthur Waterbury, M.D., Waterloo, Iowa, died April 29, 1950, after a long illness. He was born in Cedar Rapids, Iowa, August 9, 1874; graduated from the Hahnemann Medical College and Hospital, Chicago, Ill., 1899, and pursued postgraduate studies at the Chicago Postgraduate Medical School, New York University Postgraduate Medical School and Harvard Medical School.

Dr. Waterbury was formerly a member of the staff of the Presbyterian and Allen Memorial Hospitals and Pediatrician at the St. Francis Hospital of Waterloo. He was a Fellow of the American Medical Association, a member of the Iowa State Medical Society and numerous other medical organizations. He was a past President of the Waterloo City Medical Society and past President of the Iowa Clinical Medical Society. He was an Associate of the American College of Physicians by virtue of membership in the American Congress on Internal Medicine, which was merged with the College in 1926.



PAVATRINE® WITH PHENOBARBITAL

exerts two types of spasmolysis—neurotropic and musculotropic—in addition to providing central nervous system sedation. Pavatrine with Phenobarbital is non-narcotic and effective on oral administration. G. D. Searle & Co., Chicago 80, Illinois.

SEARLE

RESEARCH IN THE SERVICE OF MEDICINE

Ann Woodward
Director

How Long Should The Doctor's Day Be?

AS LONG as patients require and his energies will serve him? As short as he might like it? . . . OR, somewhere between—a day dictated by common sense *and made possible by planning?* Many conscientious physicians, believing they can best serve their patients by budgeting their energies, have planned accordingly *and supported their plans by engaging competent assistants.* Some choose for these posts young men whom they can train early in their own methods. Others prefer seasoned physicians to whom they can immediately delegate considerable responsibility.

Some excellent representatives of both groups are registered with us right now. Should you choose your assistant from among these candidates, a searching background study of each, plus our years of experience in judicious medical placement, is your assurance of accurate information.

Why not file our address for quick reference—today, next month, next summer?

WOODWARD *Medical Personnel Bureau*
NINTH FLOOR . 185 N. WABASH . CHICAGO 1
Our Fifty-fourth Year

WANTED!

Back Issues of

ANNALS OF INTERNAL MEDICINE

Good used copies of the *following* issues are now needed. Only those issues which are currently being advertised can be accepted.

$1.00 each for

Vol. I, No. 1—July, 1927
Vol. I, No. 3—August, 1927
Vol. I, No. 4—October, 1927
Vol. I, No. 5—November, 1927
Vol. I, No. 6—December, 1927
Vol. I, No. 7—January, 1928
Vol. I, No. 8—February, 1928
Vol. I, No. 9—March, 1928
Vol. II, No. 4—October, 1928
Vol. II, No. 5—November, 1928
Vol. IV, No. 8—February, 1931
Vol. IV, No. 10—April, 1931
Vol. VII, No. 2—August, 1933
Vol. XXXII, No. 4—April, 1950

$.75 each for

Vol. XXXII, No. 2,—February, 1950

Address journals to:

E. R. LOVELAND, Executive Secretary
4200 Pine Street Philadelphia 4, Pa.

Symbols of Fellowship

Every Fellow of The American College of Physicians prizes his Fellowship and should make use of these symbols to remind him, his associates and his patients of the ideals, aims and accomplishments of the College.

FELLOWSHIP KEY

This beautifully designed charm, bearing the seal of the College, is 10K solid gold and embossed in the College colors. Shown actual size. Initials of Fellow and date of election engraved on back at no extra charge. *Price, including tax, delivered, $7.50.*

FELLOWSHIP PLEDGE

All Fellows subscribe to this pledge at time of induction. Engraved with artist's outlined initials and the College seal in color; mounted and framed, with line for Fellow's signature. Ideal for reception room or office. *Price, framed and delivered, $6.00.*

FELLOWSHIP CERTIFICATE FRAME

The Fellowship Certificate furnished without charge to newly elected Fellows should be protected and displayed in the official, distinctive frame. Similar in design to Pledge frame; attractively finished in gold. Shipped without glass. *Price, delivered, $4.00.*

AS A GIFT

To a Fellow, for that birthday or anniversary, or for any occasion, the Fellowship Key, Fellowship Pledge or Certificate Frame is ideal. These symbols of Fellowship become treasured possessions; reminders of high purpose and achievement.

Order now from:

The American College of Physicians
4200 Pine Street, Philadelphia 4, Pa.

Please Mention this Journal when writing to Advertisers

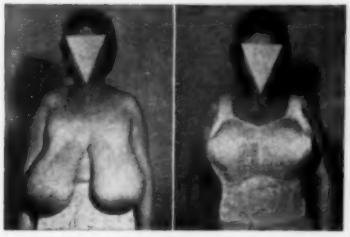
The only booklet of its kind . . .

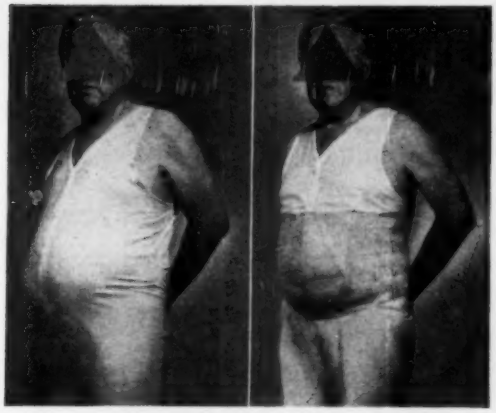
This booklet is a summarization of practical therapeutic information on the use of supports in modern medical practice. A series of 23 illustrated case abstracts cover such conditions as:

Protruded intervertebral disc, poliomyelitis, low-back pain, fatigue and lordotic posture, lumbosacral sprain, tumor of the spine, tuberculosis of the spine; hernia, fasciomyositis, postural syndrome, visceroptosis, colostomy; pendulous breasts, mastectomy, thoracoplasty; gravidity, normal and following spinal fusion.

Reference is made to Spencer experimental work in control of postural hypotension, later reviewed in *Annals of Internal Medicine* 30: 307-329 (Feb.) 1949.

THREE SETS OF THE EIGHTY-NINE ILLUSTRATIONS IN THIS BOOKLET





Send coupon for your FREE copy

MAIL coupon at right—or PHONE a dealer in Spencer Supports (see "Spencer corsetiere," "Spencer Support Shop," or Classified Section) for information.

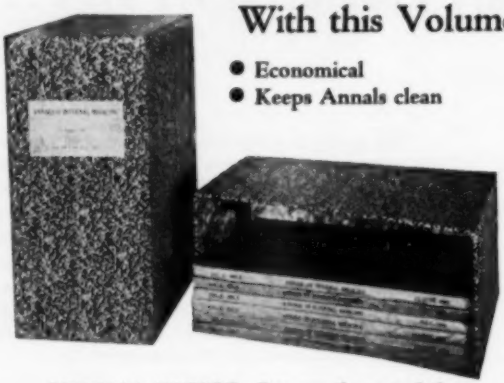
SPENCER, INCORPORATED
127 Derby Ave., Dept. IM, New Haven 7, Conn.
Canada: Spencer, Ltd., Rock Island, Que.
England: Spencer, Ltd., Banbury, Oxon.
Send booklet, "Spencer Supports in Modern Medical Practice."
Name ..... M.D.
Address .....
.....
11-50

individually designed SPENCER® SUPPORTS

PRESERVE

Your ANNALS OF INTERNAL MEDICINE

With this Volume File



- Economical
- Keeps Annals clean
- Copies easily accessible
- Every copy in perfect order

This Volume File will keep one complete Volume, or six issues, of the "Annals of Internal Medicine" clean, orderly and readily accessible for reference. Indexed on front with name and volume number.

Sent postpaid, $1.75 each

SPECIAL NOTICE: Because the cost of the Permanent Binders (Loose-leaf Volume Binders) has increased out of all proportion to their worth, we have been forced to discontinue supplying them. These economical, easy-to-use Volume Files are especially recommended.

AMERICAN COLLEGE OF PHYSICIANS
4200 Pine Street
PHILADELPHIA 4, PA.

THE
MEDICAL
PROTECTIVE
COMPANY
FORT WAYNE,
INDIANA

Professional Protection Exclusively since 1899

Hyland Laboratories Announces the Immediate Availability of

Irradiated

ANTI-HEMOPHILIC PLASMA

(Human)

For the Treatment of the Prolonged Bleeding Time in Hemophiliacs

A single dose will usually return the clotting time of hemophiliacs to within normal limits for a period of hours and longer. Doses may be repeated as needed. Must be injected intravenously for full therapeutic effect.

The plasma is rapidly processed from freshly drawn blood and brought to the dried state — for retention of activity — within a few hours.

Contains no preservative but is treated with ultraviolet radiation to destroy possible bacterial and viral contaminants, including the agent or agents of viral hepatitis. Meets requirements established by the National Institutes of Health and is distributed under license No. 140.

Single-dose package includes 50cc Anti-Hemophilic Plasma in the dried state and a suitable diluent. Because stocks are not unlimited, please ask your regular source of supply to order directly from Hyland East or West Coast depots —addresses below.

Additional Information Available on Request

HYLAND LABORATORIES — Biologicals

4334 Sunset Blvd., Los Angeles 27, Calif. 26 Vark St., Yonkers 1, New York, c/o Arlington Chemical Co.

FOR RAPID RELIEF

OF

MASSIVE EDEMA

(Archives Int. Med., Jan. 1950)

PHYSICIANS SHOULD HAVE

SOUTHEY-LEECH TUBES

ON HAND

$10.00 per set—6 tubes and trocar, with drainage tubing.

Send cash, check or money order to:

THE BRIGGS COMPANY

82 Waterman Street

Providence 6, R. I.

FOR DIABETICS

CELLU UNSWEETENED FRUITS

PACKED IN NATURAL JUICE OR WATER

Brighten your diets with Cellu Canned Fruits. Over 16 varieties packed either in natural juice or water without added sugar. Food values are printed on labels to simplify diet measurements.

WRITE FOR CELLU CATALOG

LOW CARBOHYDRATE

CELLU Dietary Foods

CHICAGO DIETETIC SUPPLY HOUSE Inc.

1750 West Van Buren Street Chicago 12, Illinois

INDEX TO ADVERTISERS

November, 1950

Abbott Laboratories 33
American Hospital Supply Corp. (Baxter Laboratories) 39
Ames Company, Inc. 6
Appleton-Century-Crofts, Inc. .. Second Cover
Beck-Lee Corporation 31
Brewer & Company, Inc. 28
Briggs Company, The 45
Buffington's Inc. 4
Burnham Soluble Iodine Company 47
Burroughs Wellcome & Co. (U. S. A.) Inc. 15
Cambridge Instrument Company, Inc. 5
S. H. Camp & Company 34
Chicago Dietetic Supply House, Inc. 45
Chilcott Laboratories 12, 13
Ciba Pharmaceutical Products, Inc. 14
Warren E. Collins, Inc. 47
Commercial Solvents Corporation 38
Davies, Rose and Company, Limited 30
Dietene Company, The 35
Flint, Eaton & Company 20
E. Fougera and Co., Inc. 32
Geigy Company, Inc. 10
Gradwohl Laboratories 47
Hall-Brooke 2
Hille Laboratories 24
Paul B. Hoeber, Inc. 3
Hyland Laboratories 45
Kelley-Koett Manufacturing Company 18
Lea & Febiger 4
Eli Lilly and Company 9
Macmillan Company, The 1
Medical Protective Company, The 44
Merck & Co., Inc. 19
O. E. M. Corporation 26
Oxford University Press, Inc. 2
Parke, Davis & Company 23
Chas. Pfizer & Co., Inc. ..... 11, Third Cover
Sanborn Company 36
Schenley Laboratories, Inc. 7, 27
Schering Corporation 17
G. D. Searle & Co. 41
Sharp & Dohme 40
Smith, Kline & French Laboratories 16, 25
Spencer, Incorporated 43
E. R. Squibb & Sons 22
U. M. A. Inc. 48
Varick Pharmacal Co., Inc. 37
White Laboratories, Inc. 21
Winthrop-Stearns, Inc. 8
Woodward Medical Personnel Bureau 42
Wyeth Incorporated 29

WILL YOU SELL

Your

APRIL, 1950

ANNALS of INTERNAL MEDICINE ?

Copies of the April, 1950, issue of the Annals of Internal Medicine are urgently needed.

We will pay $1.00 each for good used copies, if sent *now* to:

E. R. Loveland, Executive Secretary
AMERICAN COLLEGE OF PHYSICIANS
4200 Pine Street
PHILADELPHIA 4, PA.

A.C.P. POSTGRADUATE COURSES

Course No. 7, GASTRO-ENTEROLOGY: Henry L. Bockus, M.D., F.A.C.P., Director; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; December 4–9, 1950.

Course No. 8, SELECTED ASPECTS OF CLINICAL HEMATOLOGY: William Dameshek, M.D., F.A.C.P., Director; New England Center Hospital and Tufts College Medical School, Boston, Mass.; December 11–16, 1950.

Course No. 9, MODERN TRENDS IN DIAGNOSIS AND TREATMENT OF HEART DISEASE: William G. Leaman, Jr., M.D., F.A.C.P., Director; Woman's Medical College of Pennsylvania and Other Philadelphia Institutions, Philadelphia, Pa.; January 22–27, 1951.

Fees: $30.00, A.C.P. Members; $60.00, Non-members.

For details and application blanks address the

EXECUTIVE SECRETARY
AMERICAN COLLEGE OF PHYSICIANS
4200 Pine Street Philadelphia 4, Pa.

A complete line for clinical laboratories devoted to all branches of chemistry, bacteriology, hematology, and parasitology. Tested and checked in our own clinical laboratories. Purity warranted. Our facilities assure prompt shipment of large or small orders. Inquiries invited.

COMPLETE CATALOG

Reagents catalogued alphabetically—also according to subjects and techniques, plus medical reference guide. Catalog comprises full line blood testing sera including anti-Rh, anti-M and anti-N_1 also reagents for Wassermann, Kline, and Kahn tests. Write for your copy. FREE ON REQUEST.

and Medical Reference Guide

GRADWOHL LABORATORIES

R. B. H. Gradwohl, M. D., Director

3514 Lucas Av. St. Louis, Mo.

ANNOUNCING

LUGOLCAPS a capsule equivalent to Lugol's solution for use in hyperthyroidism—tasteless and convenient.

Bartels, E. C. and Johnson, A. C.* administered one LUGOLCAP daily with antithyroid drug to 25 consecutive patients during the final 21 days of preoperative antithyroid treatment. In each case satisfactory involution of the gland was produced.

LUGOLCAPS are suggested also for use in recurrent hyperthyroidism and in mild hyperthyroidism where medical treatment is the method of choice, one LUGOLCAP daily.

1 LUGOLCAP = 0.3 cc's av. U.S.P. dose Lugol's = 7½ drops
Bottles of 21 and 100

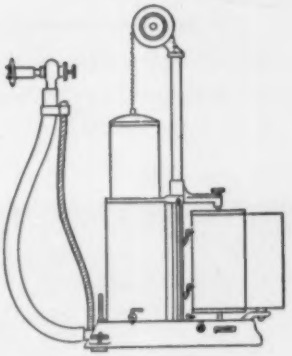
* Lahey Clinic Bulletin, January 1950.

Write for reprint and sample.

Burnham Soluble Iodine Company

Auburndale 66, Massachusetts

RESPIRATORY FUNCTION TESTS



MAY HELP YOU TOO!

The increasing importance attached to the detection and treatment of pulmonary disorders in their early stages has resulted in the opening of a large number of new chest clinics all over the country. Private investigators too have increased as the facts became known that large numbers of unsuspected cases were being discovered.

The Collins Respirometer is largely responsible for the ease in which these tests can be made. It's as simple to run as a metabolism apparatus. In fact, it's ideal for B.M.R.'s also.

Investigate now—maybe a respirometer could help you too.

ALSO—Collins Vitalometer for vital capacity determinations and the Collins Chain-Compensated Gasometer for respiratory quotient and CO_2 and O_2 values.

Write for circular V which describes the Respirometer—what it does and sample spirograms.

WARREN E. COLLINS, INC.

Specialists in Respiration Apparatus

858 HUNTINGTON AVE., BOSTON 15, MASS.

THE U.M.A. THERMOCOUPLE

is extremely important for determining the presence of Peripheral Vascular Disease.

For taking skin and subsurface temperatures instantaneously and accurately the U. M. A. THERMOCOUPLE is the standard the world over.

Any number of consecutive direct readings can be rapidly taken without lag or calculations of any kind.

Accurate, soundly engineered and sturdily built to give a long period of carefree service. No batteries.

Indicates instantly in Fahrenheit and Centigrade.

The U. M. A. THERMOCOUPLE is extremely low in price **$125.00**

At your Dealer or send for literature.

The COLLENS SPHYGMO - OSCILLOMETER

(not illustrated)

is the most important diagnostic aid in Peripheral Vascular Diseases. A blood pressure apparatus and an oscillometer in one instrument. **$36.00**

The COLLWIL INTERMITTENT VENOUS OCCLUSION APPARATUS

(not illustrated)

is the proved and accepted single and automatic therapy whenever impairment of arterial circulation of the limbs occurs. **$177.00**

U. M. A. Inc.

56 Cooper Square, New York 3, N.Y.

Algonquin 4-0924

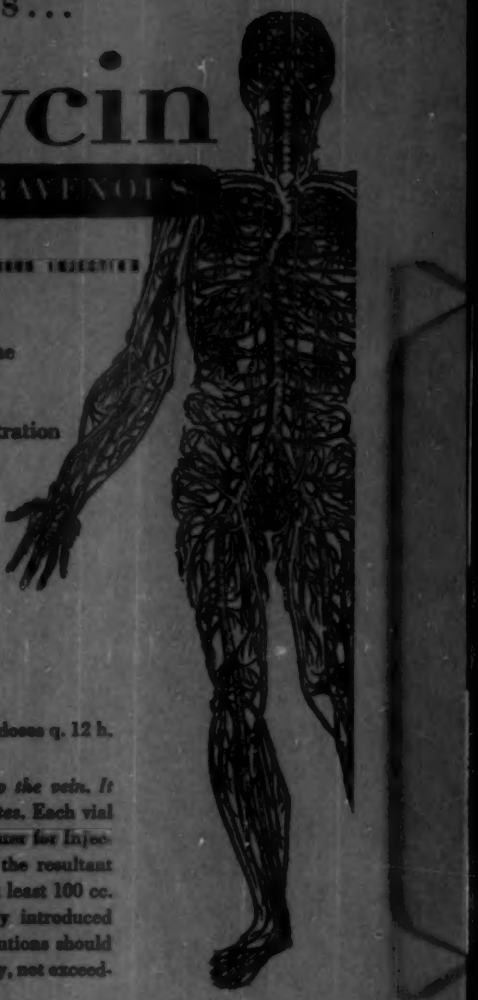
Pfizer announces...

Terramycin

for hospital use only

INTRAVENOUS

CRYSTALLINE TERRAMYCIN HYDROCHLORIDE FOR INTRAVENOUS INJECTION



Affords the advantages of intravenous therapy with the newest of the broad-spectrum antibiotics in:

... those conditions and cases in which oral administration is not feasible;

... severe, fulminating or necrotizing infections (by rapidly producing high serum concentrations);

... pre- and post-operative prophylaxis;

... peritonitis.

Dosage and Administration:

0.5 Gm. to 1.0 Gm. of Terramycin Intravenous in divided doses q. 12 h. has been found adequate for most acute infections.

Terramycin Intravenous should be injected directly into the vein. It is never given by the intramuscular or subcutaneous routes. Each vial is dissolved in sterile 5% Dextrose for Injection, USP, Water for Injection, USP, or Physiological Saline Solution, USP, and the resultant clear solution further diluted to give a final volume of at least 100 cc. When desired, Terramycin Intravenous may be directly introduced into solutions for continuous drip infusion. Injection solutions should not contain more than 5 mg. per cc. and are injected slowly, not exceeding 100 cc. in five minutes.

Supplied: 10 cc. vials containing 250 mg. of Crystalline Terramycin Hydrochloride with sodium glycinate as a buffer.
20 cc. vials containing 500 mg. of Crystalline Terramycin Hydrochloride with sodium glycinate as a buffer.

Antibiotic Division Pfizer CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

ANNALS OF INTERNAL MEDICINE

Official Periodical of the American College of Physicians

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital, Baltimore 1, Md.

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

The Annals of Internal Medicine is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

Manuscripts. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

Reprints. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

Reviews. The Annals will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

Subscription. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by volume or by year. Volumes will consist of approximately 1,300 pages. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.25. Members of the American College of Physicians receive the Annals of Internal Medicine in connection with the payment of annual membership dues, of which nine dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. Stroud, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

Business Correspondence. All correspondence relating to business matters, advertising, subscriptions to the Annals, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

Associate Editors

David P. Barr ..... New York
Robert A. Cooke ..... New York
James H. Means ..... Boston
O. H. Perry Pepper ..... Philadelphia
James J. Waring ..... Denver

Assistant Editor

Paul W. Clough ..... Baltimore

EDITOR
Maurice C. Pincoffs, M.D.
University Hospital
Baltimore 1, Md.

EXECUTIVE SECRETARY
Edward R. Loveland
American College of Physicians
4200 Pine Street, Philadelphia 4, Pa.

Lancaster Press, Inc., Lancaster, Pa.